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THE CLINICAL CONCEPT OF REINFECTION IN SYPHILIS

A CRITIQUE BASED ON FIVE CASES, THE REPORTED LITERATURE AND A STUDY OF EARLY RELAPSE *

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The material for this study includes a survey of 2,439 patients with syphilis, of whom 913 had early infections in the primary or secondary stage. In this series, 56 patients were discovered who presented various forms of cutaneous and mucosal relapse. These have been considered and reported on separately.[1] In the series were also 4 cases of possible reinfection, 2 from departmental and 2 from private records, and 2 additional private cases which illustrate certain problems that arise in the attempt to differentiate clinically between what Balzer,[2] Hecht,[3] Bernard [4] and, recently Lortat-Jacob, Roberti and Poumeau-Delille [5] called pseudoreinfection and true reinfection. As pseudoreinfection is essentially relapse, we were impressed with the differential significance of this problem, and from a review of the literature, our study of relapse and the 6 illustrative cases mentioned offer a critique of the problem of clinical differentiation of reinfection from the confusion elements in relapse. We believe that eagerness to establish the verity of reinfection as a proof of cure and to add to the volume of cases of this much desired consummation has led to much uncritical reporting of alleged reinfections. In the light of our experience, we do not feel that even the recent critical review by Halley and Wasser-

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1. Stokes, J. H.; Besancon, J. H., and Schoch, A. G.: Infectious Recurrence and Mucocutaneous Relapse in Syphilis: Diagnosis, Public Health Significance and Relation to Treatment, J. A. M. A. **96**:344 (Jan. 31) 1931.

2. Quoted by Bernard, R.: Bruxelles-méd. **7**:72 (Nov. 7); 105 (Nov. 21) 1926.

3. Hecht, H.: Die kombinierte Abortivbehandlung der Syphilis, Arch. f. Dermat. u. Syph. **126**:327, 1919.

4. Bernard, R.: Réinfection syphilitique: pseudoréinfection-superfection, Bruxelles-méd. **7**:72 (Nov. 7); 105 (Nov. 21) 1926.

5. Lortat-Jacob, L.; Roberti, J., and Poumeau-Delille: Les réinoculations syphilitiques, Ann. de dermat. et syph. **1**:2 (Jan.) 1930.

man,[6] the most elaborate in the American literature, takes sufficient account of certain considerations that will still further reduce toward a possible vanishing point the concept of reinfection of a completely sterilized human being with syphilis.

Reinfection is a comparatively rare event in the course of syphilis today. In our series, reinfection occurred not oftener than 4 times in 2,439 cases, or once in 609 cases. White[7] reported 1 in 375 cases; Driver,[8] 1 in 384 cases; Cederkreutz,[2] 1 in 1,586, and Bernard,[4] 1 in 600. Reinfection occurred in our series once in 228 cases, in comparison with the frequency of primary and secondary syphilis. Moore and Kemp[9] gave a frequency of approximately 1 in 131 cases of primary and secondary syphilis. From the practical standpoint it is difficult to imagine that the incidence of subsequent exposure of persons with syphilis to risk of reinfection falls to as low a figure as 1 in 710 cases, which is the average of the foregoing figures for frequency of reinfection exclusive of those involving only early syphilis. It therefore follows that few exposed persons are reinfected, and if reinfection is a criterion of cure, few indeed are cured.

Mucocutaneous relapse, on the other hand, is a distinctly common occurrence in the early years of a syphilitic infection. In our experience it is at least thirteen times as common as reinfection, even by lax criteria such as we are employing at the outset of this discussion for purposes of argument. Relapse is fourteen times as common as reinfection in comparison with early syphilis in our series, and the same figure holds for the relation of relapse and reinfection to primary syphilis alone. If the criteria for valid reinfection in our own group are made stricter, as they presently will be, the comparative frequency of relapse rises rapidly. Of the four cases of possible reinfection with which we begin this study, not one, as we see it, will remain "airtight" at the end.

THE IMMUNOLOGIC CONCEPTIONS

Chesney's[10] monographic review and Harrison's[11] recent summary of the literature on reinfection, reinoculation and superinfection from

6. Halley, C. R. L., and Wasserman, H.: Second Infection in Syphilis, Arch. Int. Med. **41**:843 (June) 1928.

7. White, C. F.: Reinfection in Syphilis: With Observations on Twenty-Eight Cases, Brit. M. J. **2**:509 (Oct. 20) 1917.

8. Driver, J. R.: Reinfection in Syphilis, J. A. M. A. **83**:1728 (Nov. 29) 1924.

9. Moore, J. E., and Kemp, J. E.: The Treatment of Early Syphilis: Clinical Results in 402 Patients, Bull. Johns Hopkins Hosp. **39**:16 (July) 1926; The Treatment of Early Syphilis: The Wassermann Reaction in Treated Early Syphilis, ibid. **39**:36 (July) 1926.

10. Chesney, A. M.: Immunity in Syphilis, Baltimore, Williams & Wilkins Company, 1927.

11. Harrison, L. W.: Review of Experimental Research in Syphilis and Its Possible Application to Man, Brit. J. Ven. Dis. **5**:173 (July) 1929.

the experimental standpoint have rendered unnecessary more than a condensed statement at this point to assist in comprehension of the clinical problem. The forthcoming papers of Wade Brown and Truffi at the International Congress of Dermatology and Syphilology will likewise, presumably, cover this field for both experimental animal and man. The principles illustrated may be briefed as follows:

1. Two distinct schools of thought exist with reference to the significance of reinfection in the rabbit. Neisser,[12] Kolle,[13] Frei[14] and Prigge[15] maintained that resistance to reinfection is dependent on persistence of the original infection. Inability to reinoculate, therefore, to them, means failure to cure. Chesney and Kemp,[16] Voegtlin and Dyer,[17] Uhlenhuth and Grossmann,[18] Manteufel and Richter,[19] Worms[20] and Brown and Pearce,[21] on the other hand, maintained that an actual resistance to reinfection develops, independent of the mere persistence of spirochetes, and that an animal may be apparently immune to second infection while coincidentally free from the first infection.

2. In the process of development of these opposing concepts, a variety of important facts have come to light as follows:

(*a*) Shortly after the development of a primary lesion a second primary lesion cannot be produced by reinoculation. This involves the original Neisserian conception of anergie or resistance and chancre immunity.

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12. Neisser, A. L.: Arb. a. d. k. Gsndhtsamte. **37**:1, 1911.

13. Kolle, W.: Ueber der Schutzwirkung der Antisyphilitika (Arsenderwati, Queksilber und Wismut) gegenüber der experimentellen Syphilisinfektion, Deutsche med. Wchnschr. **50**:1074 (Aug. 8) 1924.

14. Frei, W., quoted by Harrison, L. W.: Brit. J. Ven. Dis. **5**:173 (July) 1929.

15. Prigge, R.: Immunity Results of Experimental Investigation of Syphilis, Therap. d. Gegenw. **70**:385 (Sept.); 447 (Oct.) 1929; abstr., Ven. Dis. Inform. **2**:75 (Jan. 20) 1930.

16. Chesney, A. M., and Kemp, J. E.: Experimental Observations on the "Cure" of Syphilis in the Rabbit with Arsphenamine, J. Exper. Med. **39**:553, 1924; Studies in Experimental Syphilis: III. Further Observations on the Possibility of the Cure of Syphilis in the Rabbit with Arsphenamine, ibid. **42**:17, 1925.

17. Voegtlin, C., and Dyer, H. A.: Reinoculation as a Criterion of Cure of Experimental Syphilis, with Reference to Arsphenamine, Neoarsphenamine, and Sulpharsphenamine, Pub. Health Rep. **40**:2511, 1925.

18. Uhlenhuth, P., and Grossmann, H.: Zur Frage der Immunität bei Syphilis mit besonderer Berücksichtigung experimenteller Untersuchungen am Kaninchen, Ztschr. f. Immunitätsforsch. u. exper. Therap. **55**:380, 1928.

19. Manteufel, P., and Richter, A.: Beiträge zur experimentellen Syphilisforschung, Deutsche med. Wchnschr. **52**:2113, 1926.

20. Worms, W.: Erscheinungslos verlaufende experimentelle Syphilisinfektion beim Kaninchen und Affen, Deutsche med. Wchnschr. **52**:785, 1926.

21. Brown, H. W., and Pearce, L.: Superinfection Experiments with Treponema Pallidum, Proc. Soc. Exper. Biol. & Med. **18**:255, 1921.

(b) This "chancre immunity" is dependent on a reaction of the tissues and not on the mere presence of the organism.

(*c*) Inoculation in certain tissues (vide the cornea) does not protect against inoculation in other sites (vide the testis), but certain tissue inoculations have greater general protective value than others.

(*d*) An animal may harbor a syphilitic infection without reacting to it (Manteufel and Richter [19] for the rabbit and Kolle and Schlossberger [22] for the mouse).

(*e*) In rabbits made carriers of infection by intravenous inoculation, the lymph nodes are infected; however, the rabbits may be reinoculated with the same strain of organism while still carrying the original infection in their lymph nodes and develop typical syphilomas of the testicle (scrotal chancres).

(*f*) Reinoculation of the rabbit on the site of a previous testicular chancre by an homologous strain of *Spirochaeta pallida* may take place in a proportion of instances decreasing as the age of the infection increases. A larger proportion can be infected with a heterologous than with a homologous strain late in the disease (more than ninety days after first infection).

(*g*) Nonappearance of clinical lesions in animals after reinoculation is not a proof of failure to reinfect.

(*h*) "Chancre immunity," the resistance to the development of a new chancre on reinoculation, is perhaps similar in kind to the slowly developed later absolute immunity to reinfection, but is less in degree, so that with only chancre immunity, the animal may be reinfected, as subsequently proved by inoculations made post mortem from its lymph nodes and viscera.

(*i*) The development of the complete or highest degree of immunity to reinfection varies in time with different individual animals, and may be late or early, depending on their constitution. There are intermediate cases in which the reinoculated organisms may penetrate only to the adjacent lymph nodes, or remain sequestered at the site of the second inoculation.

(*j*) Superinfection in rabbits after subcurative doses of the arsphenamines (Brown and Pearce [23]) may take place while the original

22. Kolle, W., and Schlossberger, H.: Die Persistenz der Syphilisspirochäte im Mäusen während langer Zeiträume, Deutsche med. Wchnschr. **54**:129 (Jan. 27) 1928.

23. Brown, H. W., and Pearce, L.: Superinfection in Experimental Syphilis Following the Administration of Subcurative Doses of Arsphenamine or Neoarsphenamine, J. Exper. Med. **30**:553 (May 1) 1921.

infection remains latent, and the lesions of the superinfection may so precisely resemble those of the original infection that they cannot be distinguished from each other without knowledge of the chronology and localization factors.

In the attempt to apply these concepts to man, great caution must be exercised. None the less, they have a decided suggestive value that it is permissible to bring to attention here, under the following heads:

1. Immunity to chancre has been believed to exist in man as far as cutaneously inoculated infections are concerned. A long series of observations has shown that resistance or nonreaction to reinoculation begins about the second week of the chancre and persists for an undefined period of months and probably years. The existence of a higher degree of immunity is inferred from the long latency and presumed resistance to reinfection in many, but it is as yet imperfectly defined and of uncertain duration.

2. Relapse is more prone to occur in man than in animals (Brown and Pearce) and is a function of decline in local tissue resistance which, however, is gradually enhanced by repeated increments in successive relapses until it becomes sufficient to hold the infection in check for a latent period varying in duration with the individual and with other factors, such as injury. While this resistance to multiplication of the organisms and spread of the infection from any local focus is sufficient, when highly developed, to prevent clinical manifestations, the infection is not abolished, but continues, in a high proportion of cases, indefinitely.

3. Subcurative treatment modifies the situation to the extent of destroying the multiplying organisms or reinforcing the defense at any given point, so that healing and disappearance of lesions take place; but it does not prevent the later reappearance of the original lesions or the further development of new ones when the relapse cycle again permits the organisms to resume multiplication and to overwhelm the tissue defense.

4. The arsphenamines are particularly at fault in that their influence, being largely exerted on the organisms rather than on the tissue defense, offers only the most transient protection against recurrence when the multiplication of organisms again begins. Accordingly, relapse is particularly to be expected in patients treated with the arsphenamines in subcurative doses. Relapse, and not reinfection after sterilization, is, therefore, the more to be expected result of short courses of treatment with arsphenamine unsupported or imperfectly supported by resistance-stimulating drugs such as have been used in many so-called abortive cures.

5. Observation of mucocutaneous relapse tends to indicate that it is an incident of the first two years of a syphilitic infection in man. Alleged reinfections reported within this period that may be confused with mucocutaneous relapse, especially during treatment with arsphenamine, are *ipso facto* open to suspicion of being relapses (see accompanying table).

6. It has been possible to demonstrate (Warthin [24]) that much that has passed for cure in the arsphenamine era is in reality merely asymptomatic latency. Warthin stated that he has yet to see the first case of proved cure in man; that the effect of modern treatment is simply to produce a premature latency, and that superinfection is the proper term to apply to the alleged cases of reinfection which have been reported in man.

7. Superinfection with generalization from an inoculation focus and the production of typical primary and secondary lesions and with recovery of the *Spirochaeta pallida* has long been in doubt in man. If the work of recent Japanese investigators, including that of Akatsu,[2] Yakota,[2] Adachi [25] and Hashimoto,[2] is confirmed, superinfection following a course indistinguishable from reinfection or relapse will become an established entity in syphilis in man. Alleged reinfections occurring soon after the original infection will be interpretable as relapses, while those occurring years after the original infection, when general immunity has perhaps begun to decline, will be interpretable as superinfections. It will then remain a matter for separate demonstration in man, not by clinical studies in life but by studies of pathologic tissue and inoculation of human tissues into animals, to prove, exactly as has been done in the rabbit, the existence of a true "cure" or complete sterilization by treatment or otherwise.

8. A conception far more radical, though from the opposite direction, has been advanced by Kolle,[26] that man may become a carrier of *Spirochaeta pallida* in the same sense as the mouse, and that though he has never developed symptoms or reacted to the disease, he may even become a distributor of it.

In reasoning about the immunity developed in the later years of a syphilitic infection, it should be clearly understood that its duration

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24. Warthin, A. S.: Lesions of Latent Syphilis, Brit. M. J. **2**:236 (Aug. 10) 1929.

25. Adachi, Y.: On Experimental Reinoculation of Syphilis in Rabbits: II. Reinoculation Experiment in Syphilitic Rabbits; "Superinfection," Acta dermat. **4**:393, 1925.

26. Kolle, W.: Die Bedeutung der experimentellen symptomlosen Syphilisinfektion für die Erforschung der Lues—Epidemiologie und Pathologie, Centralbl. f. Bakteriol. (Abt. 1) **106**:134, 1928.

and the influence of individual constitutional factors are as yet imperfectly understood even for the animal, to say nothing of man. It is conceivable, and in fact the belief is to some extent supported by the work of Breinl and Wagner,[27] that there may be infected persons who develop only a partial immunity, such as the chancre immunity; that others may develop a complete immunity of less than lifetime duration and hence in later years may become susceptible either to reinfection or more probably to superinfection, and that some persons may, though rarely, develop even a chancre immunity of short duration and may, as apparently chronic relapsers, be in reality, chronic superinfectors. Furthermore, it is conceivable that the alteration of immunity relations by treatment, particularly incomplete or substerilizing treatment with arsphenamine, may so distort the clinical picture that relapse, reinfection and superinfection become indistinguishable from each other.

THE CLINICAL CRITERIA FOR PROOF OF REINFECTION

No better summary of the many proposed clinical criteria which today surround the concept of reinfection (or perhaps better second infection) in man has appeared in the literature than that of Bernard,[4] which is here given with comments on individual items.

1. The diagnosis of the first syphilitic infection should be incontestable—*Spirochaeta pallida,* proper incubation period after exposure, adenopathy, and a positive Wassermann reaction of the blood, appearing on from the tenth to the fifteenth day after the first appearance of the lesion. The first infection is better supported if secondary lesions develop, with a proper incubation period of not less than twenty days.

2. Treatment for the first infection should have been energetic and sufficient. Under that treatment all signs and symptoms, including the positive serologic reactions, should have disappeared. The obvious difficulty here concerns the decision as to what constitutes sufficient treatment. Our study of relapse indicates that it should not be less than twenty injections of an arsphenamine and an equal number of injections of a heavy metal for reasonable surety against a presumption of relapse.

3. Absence of clinical symptoms and serologic evidence of infection after the disappearance of the original symptoms should be observed for a period varying in the estimation of investigators. In a previous summary of this question one of us placed this period as not less than two years, and European estimates range from three months to several

27. Breinl, F., and Wagner, R.: Untersuchungen über Immunität bei experimenteller Kaninchensyphilis, Ztschr. f. Immunitätsforsch. u. exper. Therap. **60**:23, 1929.

years. Our study of relapse confirms our belief that in order to escape confusion with morphologically similar lesions of relapse, two years is an appropriate minimum free interval between the end of treatment for the first, and the onset of the second, infection.

4. The proof of "cure" of the first infection must be complete, negative reactions of the spinal fluid being included. The already weak "proofs" of "cure" are being weakened by the growing evidence for the development of cardiovascular complications traceable to the original infection in spite of prolonged and even repeated negativity of the blood and spinal fluid. Moreover, *Spirochaeta pallida* has been found repeatedly in normal spinal fluid early in the disease.

5. The proof of cure should be reinforced by a reactivation or the provocative test of Milian. One of us (J. H. S.[28]) reported the failure of negative provocative tests to demonstrate the fact of cure.

6. Between the first and the second infection there should have been no relapses.

7. The interval between the termination of treatment for the first infection and the appearance of the second chancre should be fairly long. On this point, as in 3, the differences of opinion range from a period of several months (Hell[29]) to one of five years (John[2]), or to such arbitrary figures as "longer than the duration of treatment." Again we are disposed to insist that a valid interval must be greater than that observed in the majority of our cases in which relapse occurred; in 73 per cent relapse occurred within the first year, and in 93 per cent by the end of the second year, after treatment was stopped. Even in the prearsphenamine era (Nielsen,[30] 1909) spirochete-containing lesions were recognized nine, eleven and thirteen years after infection.

8. There should be time for and the possibility of coital infection in the intervals involved. The import of denial by the patient of infectious exposure is brought out in some of our case histories.

9. The confrontation of the infected person and his source of infection are desirable.

10. The second initial lesion must be incontestable—of a normal incubation period (this evidently depends on accurately ascertained

28. Stokes, John H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1927.

29. Hell, F.: Reinduratio, Reinfectio, Superinfectio und chancriform Papeln bei Lues, Arch. f. Dermat. u. Syph. **124**:443, 1917.

30. Nielsen, L.: Papulo-erosiv Syphilitide im Mund und Schlund mit Nächweissung von Spirochaeta pallida ungefähr neun Jahre nach Infektion, Monatschr. f. prak. Dermat. **48**:53, 1909.

exposure data, which are dependent usually on the patient's statement), *Spirochaeta pallida* should be present; the serologic tests of the blood, negative at the outset, should become positive under appropriate observation (by modern tests, this may range from seven to twenty days).

11. The second chancre must appear at a different site from the first. This provision is obviously intended to do away with the possibility of monorecidive and gummatous chancriform recurrence. As pointed out in our study of relapse, there is some reason to suspect from the striking genital localization of lesions in a relapse that there is such a thing as infected terrain, as in pyogenic infections, and that on a surface so small as the penis, for example, it is a matter for question whether 1 or 2 cm., or even 5 or 6 cm., as between the glans and the shaft, is an absolute proof that "different location" means the same thing as "different origin" irrespective of the question of lymphatic drainage provided for in the next criterion.

12. The new chancre should even occur in a different lymphatic drainage from the original chancre. Hecht's views on this point should be recalled. Hecht,[3] while critically analyzing and describing various types of lesions in a relapse, including "re-erosive and chancriform papule," did not consider the site or lymphatic drainage important.

13. Satellite adenopathy should appear with the second chancre equally with the first. Our observations tend to vitiate this criterion in our estimation, because[4] only 70 per cent of chancres as we have observed them have clinically recognizable satellite adenopathy.

14. A second secondary exanthem is necessary for confirmation of the second infection. While certain observers insist on this, others maintain that strict insistence on this point would cut down the proportion of reported reinfections considerably, for few patients will, under the direction of a conscientious physician who appreciates the danger of infectiousness and the better outlook of cure by early treatment, be allowed to go on to such a confirmation. In only one case, under hospital observation, has one of us felt at liberty to watch this confirmatory episode occur.

15. The two syphilitic infections should have been observed by the same physician or at least by two competent physicians. We are inclined to insist rather on competence than on identity, and to feel that the natural prejudice in favor of a rare or significant interpretation, such as reinfection, constitutes a serious item in the subjective background of a report.

It will be apparent from this résumé that few of the criteria of reinfection escape some completely or partially invalidating criticism. In other words, a high proportion, and probably most cases of reinfec-

tion, will be, as Lacapère [31] pointed out, disputable. If this is the case for the most elaborate group of criteria yet collected, the margin of error must be still larger when fewer factors are considered. The strength of the case for reinfection in any individual instance being rather in a multiplicity or mass of disputable items than in a few irrefrangibles, we are inclined to disagree with Halley and Wasserman [6] in their disposition to adopt fewer or more lax criteria than those advanced by one of us (J. H. S. [28]) for the sake of accumulating a larger body of statistical material. We are inclined to question whether conclusions drawn from a large mass of collected cases of very doubtful derivation are more valid than those from a smaller mass subjected to a most severe though not absolutely infallible scrutiny. Halley and Wasserman, however, have performed the valuable service of sifting out through a sieve of medium mesh, so to speak, 447 cases of the 676 reported, which probably represent the increment due to unchecked observation based on enthusiasm, inexperience, eagerness to prove modern methods effective and an inadequate critical faculty.

CERTAIN COMMON GROUND AND A CONFUSION BORDERLINE BETWEEN RELAPSE AND REINFECTION

There is a tendency to dismiss as largely of historic value the clinical criteria for differentiation between the lesions in a relapse and those of alleged reinfection (Bernard [4]). Lortat-Jacob, Roberti and Poumeau-Delille [5] discussed under this head only "chancre-redux" or monorecidive, and the chancriform gumma. Hell [29] and Hecht,[3] on the other hand, likewise painstakingly developed this aspect of the critical study of reinfection from the clinical side, and discarded as unacceptable groups of cases falling under the classifications of chancriform papule, giant papule, reindurations, reerosions, etc. Bernard, in dismissing Hell's discussion and this aspect of the matter, said that treatment has reached such a stage of perfection in Belgium that mucosal syphilids are rarely seen, and hence the differential issue no longer exists. Whatever may be the state of affairs in Belgium, we do not conceive it to be such in clinical practice in the United States. Hudelo and Rabut [32] (1924) viewed the matter more as we believe it must be viewed in this country today: that the "explosion of reinfections in the months following the use of 606 and 914 must be viewed as 'false reinfections'—chancriform recidives dependent upon colonies

31. Lacapère: Àpropos d'une reinfection syphilitique: Le séro-réaction positive est le fonction du terrain de la graine, Bull. Soc. franç. de dermat. et syph. **20**:391, 1909.

32. Hudelo and Rabut: Récidives, secondaires et accidents chancriformes chez les syphilitiques traités, Presse méd. **32**:740 (Sept. 10) 1924.

of spirochetes isolated from the circulation by tissue reactions." The negativity of the Wassermann reaction of the blood in such cases has only a relative value, for "it is frequent in the course of secondary relapses." We are therefore compelled to regard as insufficiently critical the second of the two criteria of reinfection accepted as adequate by Halley and Wasserman[6]: "After an interval following antisyphilitic treatment and at a site other than that of the primary lesion of the first infection, there must develop a lesion with the characteristics of a chancre, in which the spirochetes can be demonstrated." We believe that such lesions occur also in definite categories of relapse.

CONFUSION OF PRIMARY SYPHILIS AND SECONDARY SYPHILIS

The Monorecidive.—This lesion is involved in the clinical differentiation of the primary lesions of two successive infections. In the literature it is generally spoken of as "chancre redux," a term that is satisfactory only if the term "pseudochancre redux" is discarded in favor of "chancriform gumma." The monorecidive is a recurrence in situ of the chancre. We have observed it within two weeks' lapse from treatment after seven injections of bismuth arsphenamine sulphonate. Gennerich[33] reported the appearance of a monorecidive within thirty-three days after the seventh injection of arsphenamine. Hudelo and Rabut,[32] in a series of fifty-four instances of this form of relapse, noted that 63 per cent occurred in the first year after infection and that from that point on the percentage fell from 20 in the second year to 2 or one case each in the sixth and seventh years. Cassar[34] observed a monorecidive three years after the chancre which, while not in the identical site of the original primary, was in its lymphatic drainage. The longest interval that we have observed between a probable chancriform recurrence and an original primary lesion is five years (case 1).

Critically speaking, the criteria for clearing the chancre of an alleged reinfection of the suspicion of being a mere monorecidive, then, should be an interval of at least a year, and preferably two years, between the first and second infections (83 per cent of monorecidives fall in the first two years of a syphilitic infection). The site should not be identical in the two infections, and should not even be in the same lymphatic drainage. Hecht,[35] however, pointed out how little the lymphatic drainage of the genitalia with its rich anastomoses may

33. Gennerich, W. A.: Die bisherigen Erfolge die Salvarsan Behandlung im Marinelazarett zu Wik, München. med. Wchnschr. **61**:513 (March 10) 1914.

34. Cassar, A.: Un cas de pseudo-réinfection syphilitique, Ann. de dermat. et syph. **6**:376, 1916.

35. Hecht, H.: Ein Beitrag zur Reinfiktio syphilitica, Dermat. Ztschr. **28**:193, 1919.

mean for such a criterion. In our opinion, case 2 is an illustration of the puzzling question of regional distribution of possible relapse foci about the scar of a chancre, in a case which we believed on first impression to be more probably a reinfection or superinfection than a relapse. The monorecidive, like the chancre, should be dark-field positive, but the organisms, as emphasized by Hell,[29] are fewer than in the original active chancre, a criterion rendered somewhat unreliable, however, by the relation known to exist between the number of organisms and the age of any primary lesion. We have seen a typical monorecidive thirty days after the healing of the first primary lesion contain few active organisms, but the satellite bubo swarmed with such numbers of active organisms as we have rarely seen. The chancre is supposed to have a satellite adenopathy, the monorecidive at most only a revival of the adenopathy of the original chancre. We have in one instance seen the adenopathy of a monorecidive after five injections of arsphenamine greatly exceed the adenopathy of the original chancre. The negative dark-field examination of the chancriform gumma is supposed to distinguish between this lesion and either the chancre of the reinfection or the monorecidive. In our series of relapses, of seven monorecidives with characteristic histories and sequences of time, four were dark-field positive and three dark-field negative. The chancre in reinfection is supposed to be seronegative at the onset, and later to become seropositive, while the monorecidive, being part of a recurrence, is supposed to be more frequently seropositive at first recognition. Yet one of our seven monorecidives was seronegative, though dark-field positive, and Hudelo and Rabut [32] found twenty-one seronegative monorecidives in their series of fifty-four. Our experience with relapse in general, however, indicates that it tends strongly to be Wassermann-positive at the onset, and that the demonstration that the Wassermann reaction is positive in a supposed reinfection lesion less than a week old is strong evidence in favor of relapse. Occurrence in or close to the site of the original primary lesion within a year of the original infection of a lesion seropositive on first sight is the strongest evidence, albeit subject to exception, for the identification of a monorecidive. The demonstration of *Spirochaeta pallida* or their relative number does not infallibly serve to distinguish the monorecidive from a bona fide new chancre.

Chancriform Papule.—It is a curious fact that of the supposed reinfections we have observed, the best authenticated cases from the standpoint of general criteria have had lesions least suggestive of typical hunterian chancres to mark the onset of the second infections. On the other hand, among fifty-four undoubted lesions of relapse, we observed six typical chancriform lesions as part of relapsing secondary

eruptions. Hudelo and Rabut [32] observed thirteen examples of isolated chancriform papules on the penis among the fifty-four monorecidives which they studied. An illustration of the possibilities of confusion between recurrence and reinfection, occasioned by the appearance of a chancriform papule on the scrotum near the base of the penis is given in case 3. It should be entirely possible to interpret an involuting chancriform papule which appears early in a relapse as the healing primary lesion responsible for a group of secondary mucosal lesions that developed a little later, not as part of a reinfection but as part of one and the same relapse. A case suggesting this possibility, in which the relapse with a penile papule was at least the second and possibly the third in the course of the patient's career, has been described by one of us (J. H. S.[36]).

The morphology of the chancre is so variable that it is difficult at times to decide whether or not what seems to be merely a group of erosions in an apparent second infection contains a chancre among them. Such an example was described by one of us (J. H. S.[37]); macular secondary lesions were allowed to develop, and appeared within twenty days after the first examination of a group of penile lesions of several weeks' duration, the penile lesions appearing after a proper incubation period of two weeks. They did not develop at the site of the original primary lesion, but the scar of the original primary lesion became indurated, though not eroded. This case might well fall in the type of case 2 here described, in which a group of new primary lesions or chancriform papules appeared in the vicinity of a primary scar. Case 4 is an excellent illustration of the historically probable reinfection which develops multiple erosions instead of typical penile chancres, and hence may be merely an example of recurrent mucosal secondary lesions or a superinfection.

General or Mucosal Relapse.—This is in effect an extension of the foregoing differential problem into a later stage of the second infection. One encounters not infrequently, especially in a colored clientele, obvious florid secondary lesions, yet with what seems a good history of a primary infection too long before to be a probable source of the present crop of lesions. In this connection we cite a published case [38] of rupia as apparently the secondary eruption of a "historical" second infection. The question arises as to whether, in such cases, one is confronted by a reinfection or a superinfection without chancre or simply by delayed secondary lesions. We have also published [39] the

36. Stokes (footnote 28, p. 570).
37. Stokes (footnote 28, pp. 532 and 579).
38. Stokes (footnote 28, p. 764).
39. Stokes (footnote 28, p. 561).

case of a patient whose first primary and secondary lesions involuted under two injections of arsphenamine and twelve injections of mercurial oil, only to be followed four months after the cessation of treatment by a completely new outburst of the identical type of secondary eruption present in the first attack, accompanied by a chancre which was recognized as part of the original process only by its identical site. In combination with the second explosion the patient had an iritis and a neuroretinitis. Either case 1 or case 4 of the present series will serve as an illustration of some of the confusing elements in an effort to distinguish between the secondary manifestations of a first and of a second infection.

Gummatous Chancriform Recurrence.—It is this possibility of confusion that the provision of a positive dark-field and satellite adenopathy in valid second chancres and a site different from that of the original primary lesion is intended to meet. Our nearest approach to confusion from this source was in the case of a chancriform lesion observed in a tabetic patient after appropriate incubation following a probably infectious exposure.[40] The clinically perfect chancre which developed was dark-field negative, and an examination by Warthin disclosed no specific, but rather banal, inflammatory changes and no spirochetes.

OTHER DIFFERENTIAL POSSIBILITIES

For the accomplished dermatologist and syphilologist, it is probably unnecessary to mention other possibilities of confusion raised by the occurrence of chancroid, the primary indurated papule of granuloma inguinale in the colored patient (one of the best imitations of a chancre extant) and of infected herpes, ulcus acutum vulvae and banal erosions, when accompanied by evidence of a recent syphilitic infection. In a clientele of low social status and promiscuous habits, combinations of the various possibilities mentioned sometimes furnish questions requiring more than amateur analysis.

ILLUSTRATIVE CASE MATERIAL ON PROBLEMS OF REINFECTION

CASE 1.—A dentist, aged 39, contracted an extragenital chancre on the second finger of the left hand five years before the first observation by us. It was accompanied by a typical satellite bubo, but no dark-field examination was made, the lesion being recognized in the fourth week by the Wassermann reaction, which was strongly positive. Secondary lesions did not develop. The treatment for this infection consisted of neoarsphenamine, eight injections to a course, and three courses in all, separated by intervals of a year between courses. No mercury or bismuth was given. The Wassermann reaction, strongly positive with the first course, was weakly positive with the second and negative after the third course.

40. Stokes, John H.: A Spurious Chancre, Arch. Dermat. & Syph. **3**:295 (March) 1921.

After another year and a half (total, four years and a half since infection) without symptoms and with no serologic tests, he first noticed an erythematous accentuation of the scar of the chancre on his finger, which was intermittent, gradually cumulative and accompanied by edema. A sore throat, which presently became ulcerative, developed within a few days of the appearance of edema, and persisted until an injection of neoarsphenamine was given three weeks before we saw him, and following the finding of a positive Wassermann reaction of the blood. With this single injection the throat promptly healed, leaving no visible scar or other residuum when examined three weeks later, so that it could hardly have been a true gumma.

At the time of the first examination, the reinduration of the scar left by the chancre on the finger, little affected by the single dose of neoarsphenamine, was still visible as a raised, shiny plaque with a typical scarlike surface, at the site of the original chancre. Dark-field examination by aspiration of the base was negative (recall the injection of neoarsphenamine). There was no satellite adenopathy, and the general and syphilologic examination gave negative results. The Wassermann reaction of the blood was still strongly positive.

The patient was placed on a course of forty injections of bismuth arsphenamine sulphonate, whereupon the lesion on the finger disappeared. However, the Wassermann reaction of the blood was still strongly positive six months later, whereupon an examination of the spinal fluid was made, which disclosed a typical preparetic fluid as evidence of a neurosyphilis otherwise asymptomatic.

Comment.—The second lesion on the finger obviously was not that of a reinfection; the patient had of course had a longer period of freedom from symptoms than would be expected in the ordinary monorecidive form of relapse. Yet the reinduration in the scar of the primary lesion conformed to the clinical criteria advanced for a monorecidive, except for the negative dark-field examination (recall that the patient had already had a dose of neoarsphenamine since the lighting up of the scar). There was no revival of adenopathy. The lighting up of the scar was followed, after erythema and edema appeared, by another manifestation at a distance and of a secondary type—an ulcerative sore throat, which cleared up immediately following the single injection of neoarsphenamine. There were no cutaneous secondary lesions, but they might well have been aborted or cleared up by the single injection of neoarsphenamine, if mild or inconspicuous. A neurosyphilis had developed apparently as part of the second flare-up; it was probably not part of the first infection, since the Wassermann reaction even under the inadequate treatment and long periods of rest had become negative and no neurorecurrence had appeared.

It is conceivable, of course, that the recurrent lesion on the finger was a chancriform gumma, with subsequent gummatous ulceration in the throat, and that the neurosyphilis was of long standing, antedating the reinduration. A more plausible explanation, however, would seem to be that the reinduration preceding the sore throat was the focus of the relapse of a second generalization of the first infection with

delayed secondary lesions on the mucosae (compare with the case of completely lapsed primary and second crop of secondary lesions previously mentioned). The delay of fully five years between the original chancre and the monorecidive with recurrent secondary lesions illustrates how long the question of relapse may be an element of confusion in what might have passed as a reinfection, had there been a penile lesion, a slightly different situation and a new exposure. It is conceivable, but improbable, that the scar of the original chancre might have been reinoculated in the course of the patient's work, the site perhaps being susceptible, as suggested by Hecht.[3]

CASE 2.—In a man, aged 40, the chancre of his first infection had developed on the right side of the glans midway between the meatus and the frenum twelve years before examination. When the lesion was one week old, the diagnosis was

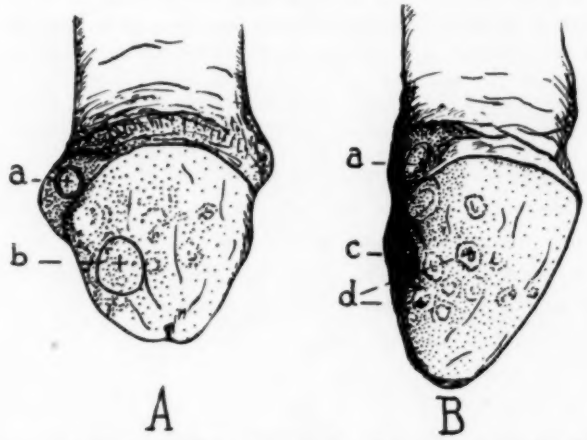

Fig. 1 (case 2).—*A*, the dorsal aspect of the penis, showing the site of the dark-field-positive chancriform papule or chancre of the supposed second infection at *a*, and the site of the original primary lesion twelve years before at *b*. *B*, the right lateral aspect of the penis, again showing the chancriform papule at *a*. The densely shaded area at the frenum, *c*, is an extension of the induration from the chancriform papule, throughout the region. In both *A* and *B* note the corymbose arrangement of small annular, papular, noneroded lesions, *d*, throughout the affected region and about the site of the old primary lesion, which was not indurated. These features present a curious morphologic mixture of reinfection and relapse, and may express a peculiar allergic state of a superinfected site.

made by an experienced syphilologist from the positive Wassermann reaction of the blood, and immediate treatment prevented the further progress of the disease. This treatment consisted of ten injections of arsphenamine and six mercurial injections followed by doses of yellow mercurous iodide. The Wassermann reaction of the blood became and remained negative in six tests after treatment was stopped, and both the blood and the spinal fluid were negative four years after infection. The patient then married, and the spouse and one child have been well.

Three weeks before we first examined him (twelve years after his first infection), a lesion began to appear on the glans. There had been repeated exposures,

with much alcoholic indulgence preceding, but the patient insisted that he had worn an unruptured condom, self-applied, each time. Later, on closer questioning, he conceded that there might have been a rupture. This admission therefore allowed appropriate incubation periods and an admitted exposure.

The lesion presented by the patient at his examination by us was remarkable in several respects. In the right coronal sulcus at the base of the frenum was a perfect little chancre with typical induration (fig. 1), an erosion 7 mm. across and a dark-field, after cleaning, containing an average of three *Spirochaeta pallida* and three *Sp. refringens* per oil-immersion field. In and surrounding the site of the old primary lesion (no scar), as pointed out by the patient, were perhaps fifteen or twenty small mosaic papules, the central five or six being annular and indurated noneroded papules, the remainder in part annular, but not notably indurated. The induration extended from the coronal chancre into the frenum, but there was neither the scar of the original chancre nor an induration of the designated site, which was at least 1.5 cm. anterior. There was a lymph node the size of a large pea in the left inguinal chain.

The results of the remainder of the examination for lesions of the skin, lymphatics, bones, viscera, heart, nervous system and special sense organs were entirely negative. The patient had felt less well than usual during the preceding week, but there were no notable symptoms of syphilis. The serologic reaction of the blood was strongly positive to the Kolmer, Kahn, Hinton and Kline tests. Treatment with bismuth and arsphenamine caused a prompt involution of the lesions.

Comment.—This case exhibits mixed clinical characteristics of reinfection and relapse, after a long interval of apparent freedom from disease and perhaps of "cure." The corymbose arrangement of indurated and nonindurated annular papules about the site of the old primary lesion has been emphasized by Hecht [3] as a feature of recurrences. Yet it has been present in at least three cases seen by us in which some of the important criteria of reinfection seemed well satisfied. The annular penile and scrotal lesion is a well recognized morphology for genital relapse and was present in 8 per cent of the total number of lesions of relapse studied by us. Yet the chancre on the frenum was perfect morphologically and contained the organisms in considerable numbers, but was not accompanied by a particularly distinctive adenopathy. Both this typical chancre and the induration of the frenum were situated at least 2 cm. from the site of the original primary lesion (patient's statement). The circumstances of exposure, primary incubation and serologic observations, while not absolutely satisfactory for reinfection, were rendered more acceptable by the long interval between the first and the apparent second infection. The heavy use of alcohol, however, which in the experience of some syphilologists predisposes to relapse, is significant here and acts further as a discrediting factor in the patient's statements as to recent events surrounding the exposures in question. It is proper to consider here, too, the possibility of reinoculation on a susceptible site as explaining some of the peculiarities of the morphology.

Case 3.—In a man, aged 30, a primary lesion developed on the corona to the left of the median line in February, 1929, following packet prophylaxis ten hours post coitu. The diagnosis was made after a positive Wassermann reaction was obtained when the patient was first seen, the duration of the lesion not being accurately known; the lesion involuted without the appearance of other syphilitic lesions, under seven weekly injections of neoarsphenamine, without other treatment. A severe attack of exfoliative dermatitis followed the seventh injection, responding in six weeks to general treatment and ten injections of sodium thiosulphate.. The patient had had no antisyphilitic treatment for five months.

Two weeks before coming under our observation, in September, 1929, he had had a plus-minus Wassermann reaction of the blood by a state board laboratory known to render insensitive reports at times. It was in the two weeks intervening since this last doubtful (positive?) test that the presenting lesion had appeared.

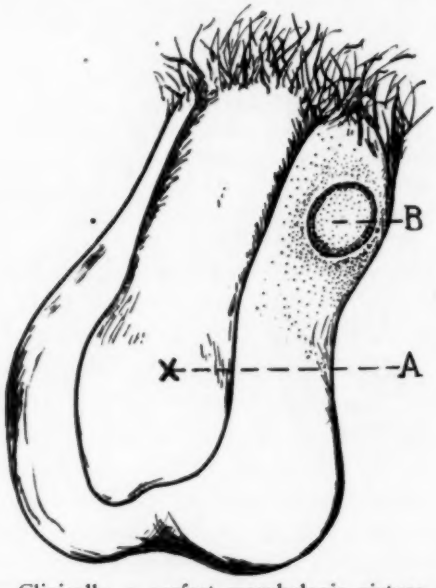

Fig. 2 (case 3).—Clinically, a perfect morphologic picture of reinfection, supported by a denial of exposure, but, on detailed consideration, quite as likely to be a solitary giant papule of a delayed secondary outbreak, in an inadequately treated patient. *A* is the site of the original primary lesion on the foreskin, which shows neither scar nor revival of activity. *B* is the dark-field-positive chancriform papule.

The lesion in question was morphologically a perfect chancre, solitary, situated about 2.5 cm. from the left base of the penis on the scrotal skin. The lesion was 1.5 cm. in diameter and perfectly round. The base was slightly raised and pale, with minute red points, a hyperemic margin and a cartilaginous induration. The secretion yielded two typical *Spirochaeta pallida* per oil-immersion field. There was a bilateral inguinal adenopathy, with a moderate general adenopathy, the enlargement of the epitrochlears being especially clear cut. The skin and mucous membranes were normal. Cardiovascular examination gave negative results, but the spleen, which should have been examined, was not. The serologic tests on the blood gave strongly positive results.

The patient denied categorically and repeatedly all sexual exposure, handling of the genitalia or contact with women since his exfoliative dermatitis five months before. Unfortunately, homosexual contact was not inquired into. Treatment was conducted elsewhere.

Comment.—Except for the precocity of the Wassermann reaction, the short time since the original infection, the inadequate treatment and the general adenopathy, with the patient's denial of exposure, this would have made a fairly convincing case of reinfection. Even dismissing as untrustworthy the patient's denials of exposure, it is still entirely possible that this was a chancriform papule of a deferred secondary outbreak, as suggested by the general adenopathy and the history of a partially positive Wassermann reaction when the lesion began to develop. The lesion, morphologically a chancre, and in a totally different site from the original primary lesion, was certainly not a monorecidive. If it was not a reinoculation, it convincingly demonstrates how perfectly a solitary papular recurrence in the genital region, which is the site of 41 per cent of the lesions of relapse in our series, can mimic the chancre. Barring the considerations mentioned, we are left with the patient's statement as the only evidence on the crucial question of exposure. The physician whom he saw when the plus-minus Wassermann reaction was recognized specifically confirmed the patient's statement that there was no visible lesion on the genitalia at that time. It is conceivable that if this was a chancriform papule of the secondary period, repression and delay may have been assisted by the exfoliative dermatitis.

Case 4.—In a man, aged 19, a primary penile lesion developed, followed by secondary lesions; the condition was confirmed by competent observation in 1925 and a positive Wassermann reaction of the blood. In sixteen months he received eight injections of neoarsphenamine and thirty-two injections of arsphenamine (606) coincidently and in alternation with twelve injections of mercuric salicylate, thirty of mercury succinimide and thirty-three of potassium bismuth tartrate, followed by forty mercurial inunctions. No complete periods of rest were allowed until this treatment was completed, and the Wassermann and Kahn reactions of the blood had been negative under treatment for more than a year. The spinal fluid showed the sole abnormality, containing seven cells per cubic millimeter fifteen months before the second infection, and was completely normal three months before the second infection. There were never any signs of a relapse, and the serologic observations of the blood likewise followed a nonrelapsing course throughout the first infection.

After a four weeks' disappearance from observation, the patient returned with what seemed at first glance to be a balanitis, but with some suggestion of a multiple papular recurrence in the coronal sulcus. Three exposures to a puella were admitted, and the first signs of a lesion had developed two days after the second, or ten days after the first, exposure. The history did not suggest herpes. The patient, however, insisted that he had worn a perfectly intact rubber condom at each exposure, and that there had been no rupture. It was not until we discovered that his Wassermann reaction of the blood, previously negative for months, had

become strongly positive that further inquiry was made, whereupon the patient recalled that the puella had applied the condoms herself, moistening them with her saliva.

The dark-field examination of the group of eroded papules about the corona was negative. None of them was a distinctive chancre, and there was no flare-up or induration at the old site near the frenum, such as occurred in case 1. There was little or no general or local adenopathy. A confirmatory Wassermann reaction was positive; the response to renewed treatment with bismuth arsphenamine sulphonate was immediate, the whole process disappearing completely in the remarkably short period of nine days without local treatment. No induration persisted, which is more like the action of bismarsen on the mucous patch than on the chancre. The Wassermann reaction of the blood became negative between the eighth and twelfth weeks of the second infection, which is the normal rate for bismarsen in a sero-positive primary infection, and remained negative until the thirteenth month. At no time did any evidence of secondary lesions appear. The spinal fluid was negative following the sixty injections of bismarsen given for the second infection, but the blood became positive thirteen months after the last injection of bismarsen, and was unquestionably, though mildly, positive (Kolmer 11, Kahn 122, Hinton 122 and Kline negative) eighteen months after the last injection. The patient resumed treatment at the time of the Wassermann relapse of the blood in the supposed second infection, and he again gave a negative reaction of the blood and spinal fluid three months later, or twenty-two months after his second infection and four years and six months after his first infection.

Comment.—Physical examinations have been performed periodically on this patient throughout the course of both infections, and in these four examinations there has become apparent, particularly within the last year, a gradual roughening, accentuation and harshening of the aortic second sound, without enlargement of the heart but with an occasionally recognizable systolic murmur, which, however, is audible over the whole base and cannot yet be diagnosed as aortic. There has been no rise in blood pressure. If this physical observation goes on to confirmation as a definite evidence of aortitis, the presumption will be strong, because of its time relations, that it is a part of the first infection carrying on under the cover of a superinfection with another strain of organism, which, as in certain of the experiments on superinfection reported by Hashimoto,[2] ran a short and comparatively benign atypical course, without the production of a typical second chancre, but rather of the papulo-erosive reinoculation lesions to be expected in the immunologic stage of recurrent secondary lesions in which the second inoculation from the puella's saliva occurred. Such interpretations remain speculative at this time, yet justify a certain skepticism as to the clinically differentiable character of relapse, reinfection and superinfection.

Case 5.—A man, aged 32, had had a dark-field-positive, sero-positive primary lesion on the dorsal surface of the corona in 1921. This lesion was said to have been diagnosed and treated, while the patient was in the Navy, with thirty-six injections of silver arsphenamine at monthly intervals. In the five year interval

between his release from treatment and his first observation in our clinic, he had had eight negative Wassermann reactions of the blood. When first seen by us in May, 1929, he presented a healed primary lesion (erythematous "button" completely epithelialized), which he said had been eroded, and which had developed seven weeks previously. The lesion was on the right side of the shaft, 2 cm. from the root of the penis. The original primary site was marked by a notchlike scar on the midline of the corona. There was a bilateral satellite inguinal adenopathy, more marked on the right side. Florid macular lesions of the trunk, mucous patches in the mouth, a condyloma ad ani (dark-field-positive) and alopecia, of one week's duration, were present. No aspiration was done on the second primary lesion. The Wassermann reaction of the blood was strongly positive.

There was a definite history of extramarital exposure five months preceding the second primary lesion, but marital exposure was of course continuous throughout this period.

Three intravenous injections of arsphenamine were given, following which the patient lapsed from treatment for ten months. On his return, a dirty, indurated ulcer, 3 cm. in diameter and of three weeks' duration, was present on the left of the frenum back of the corona. It was found to be dark-field-positive. There was a visible satellite adenopathy, which was bilateral and painless. Though the patient was not aware of it, there was a roseola over the back and trunk, but no mucosal lesions. The Wassermann reaction of the blood was strongly positive.

It developed that the patient's lapse from treatment was due to a term in jail that had occupied the entire period. The question of homosexual exposure was inquired into, but was vigorously denied.

The response to therapy was complete by the fifth injection of arsphenamine. The Wassermann reaction of the blood was still strongly positive.

Comment.—The patient, if his history is accepted as given, had had one reinfection and one ulcerative chancriform relapse with recurrent secondary lesions. The uncertainties introduced into the decision on many apparent reinfections by the necessity of relying on patients' statements is apparent from this and preceding histories. It is almost equally conceivable that the patient had had two reinfections, one from heterosexual, the other from homosexual, contact. The three chancriform lesions of his career were at widely disparate sites. The time-treatment relations of the second chancriform lesion are those appropriate to a decision of reinfection after cure, whereas those of the third lesion are appropriate to relapse from inadequate arsphenamine therapy. Yet both second and third lesions were accompanied by undoubted secondary manifestations. From such a case as this, one is inclined to infer that site is less trustworthy as a criterion of reinfection as distinguished from relapse than is often thought to be the case.

TIME-TREATMENT RELATIONS OF RELAPSE AND REINFECTION IN THE LITERATURE AND THE PRESENT SERIES

The impression that relapse and reinfection not infrequently overlap or merge in a clinically undifferentiable complex derives additional strength from certain general considerations in addition to the illustra-

tive case material of our own group as just outlined. Cutaneous and mucosal relapse, as shown by our previous experience, tends to fall, to the extent of 55 per cent, within the first year of the infection, and to the extent of 93 per cent before the end of the second year of the infection. The first two years of a syphilitic infection are therefore the stamping ground for relapse, and lesions appearing during this period must first of all satisfy the discriminating student that they are not the lesions of a relapse. Of our five cases described, only one failed to satisfy the requirement that it should occur after the period of greatest susceptibility to relapse. On the other hand, a survey of the literature included in Halley and Wasserman's summary of reported material indicates that in 58 per cent of reported cases which have been acceptable to their moderately strict standard the supposed second infections fall none the less within the two year period of predisposition to relapse.

A survey of the amount of treatment received in our fifty-six undoubted cases in which relapse occurred, previously reported,[1] indicates that 80 per cent of our patients who relapsed had received little treatment with arsphenamine and heavy metals. A comparison with the amount of treatment received by patients with reinfections acceptable to Halley and Wasserman[6] indicates that 78.8 per cent had received little arsphenamine and little heavy metal, as judged by an identical standard. Thus it appears that in many of the reported reinfections which they accepted the patients received for their first infections about the same amount of treatment as our patients with cases of relapse. This observation tends again to put a large proportion of supposed reinfections under some suspicion as being in reality relapses due to inadequate treatment.

A support of the accuracy of our data on treatment in cases of relapse, on which the foregoing statement is based, is given by the experience of Moore and Kemp,[9] who found that 88 per cent of their patients with mucocutaneous relapse had received less than twelve injections of arsphenamine. The proportion of our patients with relapse who received the same amount of treatment is 85 per cent. We thus feel justified in insisting that in judging the validity of a reinfection, account must be taken of both the time that had elapsed after the first infection and the amount of treatment received for the first infection.

ADDITIONAL WEAK POINTS IN DATA ON REINFECTION AND IN OUR OWN FIVE CASES

From a study of the literature and our own cases we believe that there are critical inadequacies in much reported material on reinfection, even when acceptable on the basis of a moderately strict standard. Notable shortcomings include the lack of data on exposure, the inability

or failure to carry the second infection from the primary into the secondary stage under observation without treatment, the lack of information with reference to adenopathy, satellite or general, and the failure to mention the state of the scar or the site of the first primary lesion. Confrontation is rarely possible, evidently, or rarely practiced, and serologic negativity in the interval between the first and second infections is often not convincingly established. Examination of the spinal fluid is seldom recorded at the close of the first infection.

Emphasis should be placed in further reporting of supposed reinfections and on the periodic complete examination of the patient during his first infection. The spleen is rarely examined or a report of its condition made, though it may well be a spirochetal reservoir. A systematic recording of cardiovascular observations on patients over a period of years may, as suggested by case 4, reveal the development of syphilitic aortitis resulting from a first infection but underlying an apparent reinfection, which thus becomes interpretable as a superinfection.

RECLASSIFICATION OF THE CRITERIA OF REINFECTION (SECOND INFECTION) INTO VARYING GRADES OF STRICTNESS

We have already cited from Bernard all the criteria that may have been proposed as significant in the identification of a second infection with syphilis. We now propose for the purposes of comparative study that these criteria, modified by our own observations, be used to determine grade I reinfections, which we shall here rate as indisputable, recognizing the fact that their acceptance as such does not preclude their later incorporation into the classification of superinfections when these shall have become clinically defined. We merely offer the criteria of grade I as a stringent differentiation from relapse.

Grade I: Practically Indisputable Second Infections from the Clinical Standpoint.—1. The original infection must be proved either by positive dark-field examination or by definitely positive Wassermann reaction of the blood.

2. A complete physical examination must have been negative for signs of syphilis, following treatment, at least two years after the onset of the first infection.

3. The Wassermann reaction of the blood must have been continuously negative for at least one year after the cessation of treatment for the first infection.

4. The cerebrospinal fluid must have been normal at or near the close of treatment for the first infection.

5. No evidence of any form of relapse of the first infection should appear in the period between the two infections.

6. A definite history of exposure preceding the second infection must be obtained.

7. A demonstration of the infectious condition of the supposed source of infection must be had by confrontation, if possible.

8. There must be an incubation period of from seven to forty days between the exposure and the appearance of the second primary lesion or lesions.

9. The second primary lesion should be on a different site and in different lymphatic drainage (if such a thing exists) from the original primary lesion.

10. No signs of activity should develop at the site of the original primary lesion.

11. A positive dark-field examination must be obtained on the second primary lesion.

12. A satellite adenopathy must be present or must develop under observation.

13. The Wassermann reaction of the blood, at first negative, must change to positive under observation while the chancre is present.

14. Secondary manifestations must appear not less than twenty days following the second primary lesion.

15. Treatment for the first infection must equal that suggested by our previously reported study of relapse, that is, twenty injections of arsphenamine and twenty injections of bismuth or mercury.

16. The time interval between the onset of the first and the second infections should be sufficient to exclude the large proportion of relapse, that is, at least two years.

17. Both infections should have been observed by the same competent physician or by two competent physicians, modern methods of examination being employed.

Grade II: Probable Second Infections from the Clinical Standpoint.—Under this head are included the following criteria:

1. There must be an indisputable first infection.

2. The patient must have been clinically and serologically negative for at least one year prior to the second infection.

3. The second primary lesion must be on a different site from the first primary lesion.

4. The second chancre must be in a different lymphatic drainage (if such a thing exists) from the first chancre.

5. No activity should appear at the site of the first chancre.

6. The dark-field examination of the second chancre must be positive.

7. Satellite adenopathy must be present.

8. As an alternative, laxity may be allowed under items 2, 4 and 7, if the Wassermann reaction of the blood changes from negative to positive under observation, or a secondary eruption develops at a proper interval while the patient is under observation.

Grade III: Possible Second Infections.—Under this head are included all the cases which fail to satisfy the requirements of grades I and II, but which satisfy the criteria of Halley and Wasserman,[6] which are as follows:

1. There must be proof that the patient had syphilis prior to the occurrence of the suspected second infection, and this proof must rest on the demonstration of spirochetes in a lesion or the occurrence of a positive Wassermann reaction in the blood serum, and not on clinical judgment alone.

2. After an interval following antisyphilitic treatment and at a site other than that of the primary lesion of the first infection, there must develop a lesion with the characteristics of a chancre in which spirochetes can be demonstrated.

Realinement of Reinfections (Second Infections) by Criteria of Three Grades of Rigidity

	Present Series	Halley and Wasserman's Series
Grade I: Practically indisputable	4 cases	236 cases
	0 cases	0 cases
Grade II: Probable	0 cases	116 cases
Grade III: Possible	4 cases	120 cases

Lest it be inferred that the criteria of grade II are too strict for practical use, it is submitted that those of Hell,[29] which constitute a fair mean among the criteria of critical European students, particularly of the phenomena of relapse, are stricter than those in grade II. We believe, on the other hand, that the second of Halley and Wasserman's criteria as quoted is an open door to the admission of cases of undoubted relapse, particularly of the chancriform papule and erosive type.

Experience with the problem of proving reinfection suggests that syphilis clinics should be better prepared for the appearance of the occasional case of reinfection; with a schedule of the indisputable type before him, each examiner, with all the resources of his organization, should set himself to test the clinical validity of the conception from every possible angle. A few such cases will go much farther in scientific value than many admitted under obviously loose interpretations and hasty work-ups. Lacking such material, the entity of second infection with syphilis in man, as distinguished from relapse, is, in our opinion, not yet indisputably established.

SUMMARY

1. The present study is based on a survey of 2,439 cases of syphilis, 913 in the primary and secondary stages. Among these there appeared 56 early mucocutaneous relapses and 4 possible second infections.

2. Reinfection, while a conspicuous element in the literature, is only one-fourteenth as common as relapse and one-sixty-seventh as common as first infection with syphilis.

3. The immunologic considerations involved in the differentiation of the lesions of a relapse from those of reinfection and superinfection as applied to both the experimental animal and to man are briefly reviewed.

4. The criteria proposed by various authors for identification of valid second infections, as summarized by Bernard, are critically reviewed.

5. The confusion borderline between relapse and reinfection, with the physical and other characteristics shared by the two in clinical practice, are described, with special reference to the monorecidive, reinduration, the chancriform papule, recurrent secondary lesions of other types and chancriform gumma.

6. Five illustrative cases, involving the differentiation of relapse, reinfection and superinfection are discussed, with emphasis on the monorecidive, the corymbose papular recurrence about the site of the chancre, the absolute mimicry of the chancre by chancriform papular recurrence, the importance and uncertainty of historical data in the interpretation of the individual case, the possibility of superinfection on an original infection progressing toward cardiovascular damage and the differentiation of second infection and relapse.

7. The factors of time and treatment in the interpretation of relapse as distinguished from reinfection are discussed for the literature and for the present series. The evidence tends to indicate that many reinfections are vitiated by their occurrence within the time period after the first infection, and with the amount of treatment for the first infection, which characterized from 80 to 93 per cent of relapses.

8. The weaknesses of existing material on reinfection with respect to historical detail, adenopathy, the scar and site of the chancre, examination of the spinal fluid and adequate physical examination are briefly summarized.

9. Reported reinfections and our own 4 cases are classified on 3 grades of strictness of criteria, with categories of indisputable, probable and possible reinfection, which are defined. Thus reclassified, it appears that there are no indisputable reinfections the evidence for which con-

forms to every requirement; about 116 conform to a moderately rigid standard and 120 conform to an average standard, which, in our opinion, is too lax to provide for confusion elements of morphology.

10. It is suggested that the highest ideal of syphilologic reporting would be the presentation of cases of "airtight" reinfection, if such a thing exists. Between enthusiasm, subjectivity and unpreparedness for the usually unexpected appearance of these cases, the large majority of reports are useless, and, in our opinion, no irrefrangible clinical entity of second infection with syphilis has been established.

EXPERIMENTAL SYPHILIS IN RABBITS

II. A COMPARATIVE STUDY OF THE KAHN AND WASSERMANN REACTIONS *

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AND
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In the first article [1] we drew the following conclusions: The Kahn test is negative in 95 per cent of nonsyphilitic rabbits and the Wassermann in 100 per cent. The Kahn and Wassermann reactions are parallel with the intensity of the syphilitic involvement. Kahn and Wassermann reactions are negative in latent experimental syphilis in rabbits. Treatment that modifies the course of experimental syphilis also modifies the Kahn and Wassermann reactions. The Kahn reaction is more sensitive than the Wassermann, as evidenced by its tendency to become positive earlier and remain positive longer. The Kahn test is somewhat more desirable than the Wassermann for use in the study and the treatment of experimental syphilis in rabbits.

METHOD

The technic and interpretation of the quantitative Kahn test were exactly the same as those employed in the previous work,[1] and the same person performed the tests. Virtually the same technic was used for the Wassermann test as was previously employed, but the tests were performed by a different technician. The organism used was the Nichols' strain of *Spirochaeta pallida*, which was obtained from the animals of the previous group. The methods of inoculation, observation and treatment employed were identically those reported.[1]

RESULTS

Before inoculation of thirty-nine of forty rabbits with syphilis, the Kahn reaction was negative on two examinations made two weeks apart. The remaining rabbit showed a reaction of 2 plus (40 units); the second specimen, for verification, was 40 units; the Wassermann reaction was 1 plus the first time and 2 plus the second time. The Wassermann reaction of the blood of thirty of these forty rabbits was negative. In

* Submitted for publication, Aug. 1, 1930.

* From the Physiological Laboratory of the University of Chicago.

1. Wakerlin, G. E., and Horrall, O. H.: Experimental Syphilis in Rabbits: I. An Experimental Study of the Kahn and Wassermann Reactions, Arch. Dermat. & Syph. **18**:539 (Oct.) 1928.

all of the rabbits in which the reactions were previously negative, they remained negative on the second test except in two that gave reactions of 3 plus on rechecking. Of the remaining ten reactions that were not negative, seven were 1 plus, two were 2 plus and one was 3 plus. On reexamination of the rabbits that showed reactions of 1 plus, two gave negative results, two 1 plus, two 2 plus and one was hemolyzed. Of the rabbits originally showing reactions of 2 plus, the reaction of one remained the same, and that of the other was negative. The result was unchanged for the rabbit that originally showed a reaction of 3 plus.

The time at which a group of eighteen rabbits showed positive (2 plus or more) Kahn and Wassermann reactions subsequent to inoculation

TABLE 1.—*Time of the Appearance of Positive Kahn and Wassermann Reactions and Palpable Orchitis in Eighteen Syphilitic Rabbits During the Weeks Following Inoculation with Spirochaeta Pallida*

	Number of Rabbits									
	4th Week	5th Week	6th Week	7th Week	8th Week	9th Week	10th Week	14th Week	17th Week	Total
Kahn	0	4	4	4	3	0	1	0	2	18
Wassermann	0	2	5	5	2	1	0	1	1	18
Orchitis	1	8	7	0	1	0	0	1	0	18

TABLE 2.—*Duration (in Days) of Positive Kahn and Wassermann Reactions, Palpable Orchitis and Chancre in a Group of Six Untreated Syphilitic Rabbits*

Rabbit	Kahn	Wassermann	Orchitis	Chancre
30	161	161	147	105
33	103	96	90	70
39	110	103	94	73
51	97	83	76	0
54	83	69	52	0
59	100	69	83	107
Averages	109	97	90	59

with *Spirochaeta pallida* is shown in table 1. The reactions of fifteen of the rabbits became positive to Kahn and Wassermann tests during the fifth to eighth weeks inclusive. In the intratesticular method of inoculation, the primary lesion, a palpable orchitis, appeared in the fifth and sixth weeks in fifteen of the animals.

The parallelism of the intensity and duration of the serologic reactions and clinical conditions of a group of six untreated syphilitic rabbits is clearly demonstrated in chart 1 and table 2. This parallelism was again manifested in the five groups of syphilitic rabbits subjected to treatment with different drugs (charts 2 to 6). The use of colloidal mercury sulphide (chart 2) shows the effect of an active antisyphilitic substance; colloidal copper sulphide (chart 3) is devoid of any action;

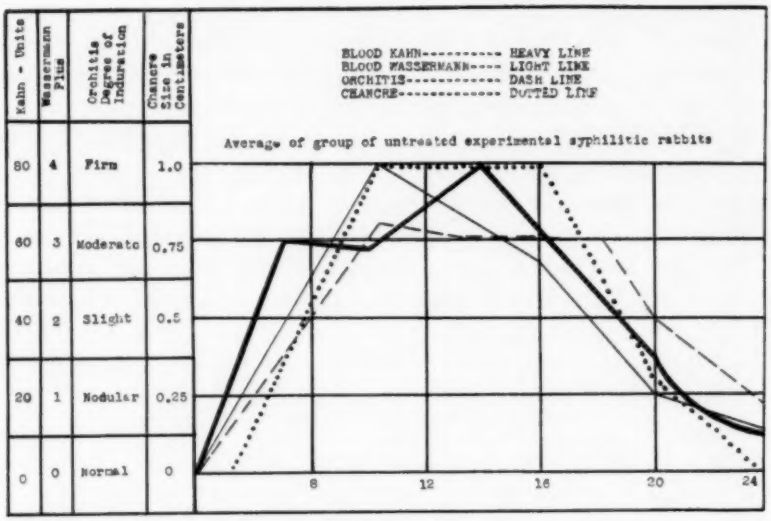

Chart 1.—The intensity and duration of the serologic reactions and clinical conditions of six untreated syphilitic rabbits.

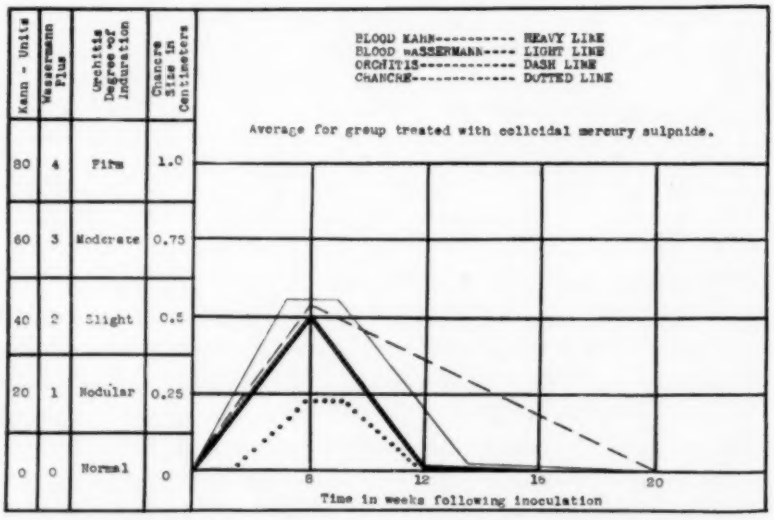

Chart 2.—This group received a total of twelve semiweekly intravenous injections of colloidal mercury sulphide, four of 2 mg. and eight of 3 mg. per kilogram. The injections were started in the eighth week following inoculation.

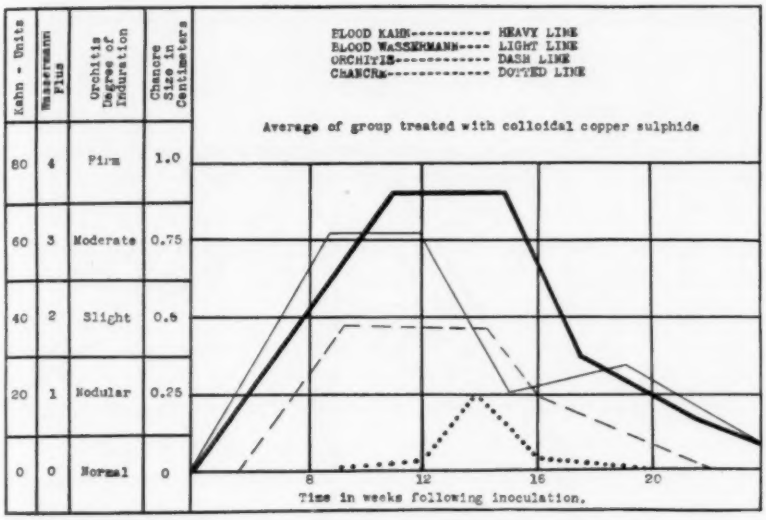
Kahn - Units
Wassermann Plus
Orchitis Degree of Induration
Chancre Size in Centimeters
BLOOD KAHN---------- HEAVY LINE
BLOOD WASSERMANN---- LIGHT LINE
ORCHITIS------------ DASH LINE
CHANCRE------------- DOTTED LINE
Average of group treated with colloidal copper sulphide
80 4 Firm 1.0
60 3 Moderate 0.75
40 2 Slight 0.5
20 1 Nodular 0.25
0 0 Normal 0
8 12 16 20
Time in weeks following inoculation.

Chart 3.—This group received twelve semiweekly intravenous injections of the colloid, four of 0.7 mg. and eight of 1 mg. per kilogram. The injections were started in the eighth week following inoculation.

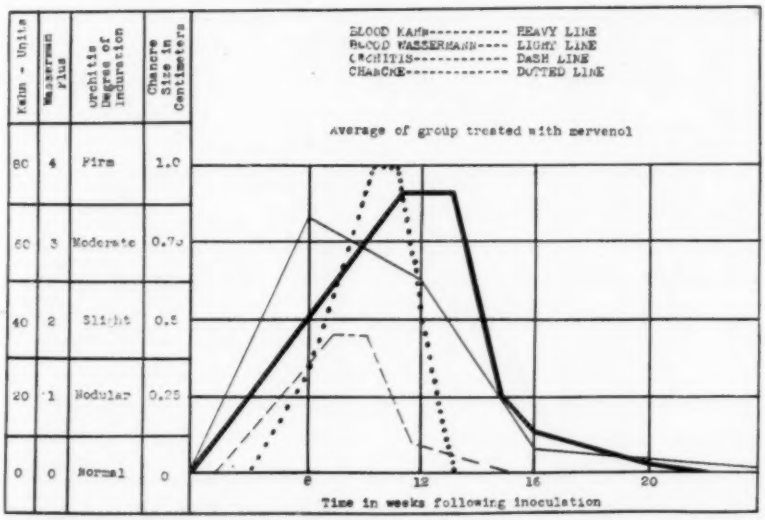

Chart 4.—This group received twelve semiweekly intravenous injections of colloidal mercury sulphide and colloidal copper sulphide in equimolecular proportions, four of 1.3 mg. and eight of 2 mg. per kilogram. The injections were started in the eighth week following inoculation.

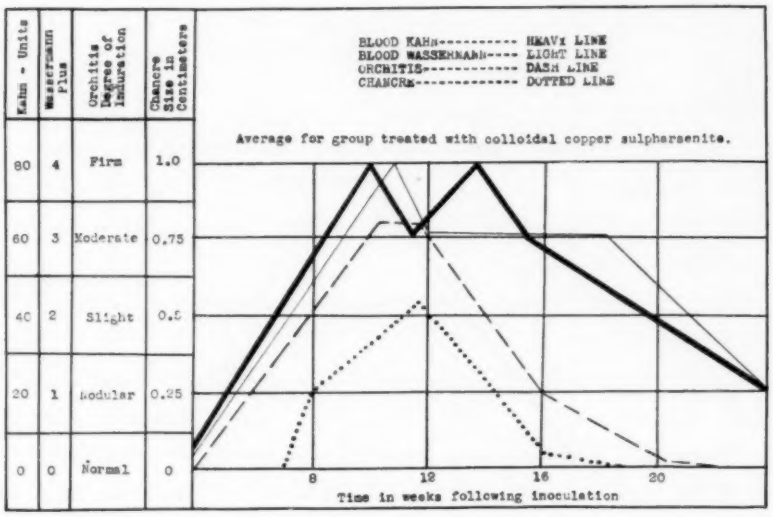

Chart 5.—This group received four weekly intravenous injections of colloidal copper sulpharsenite, each of 7.5 mg. per kilogram.

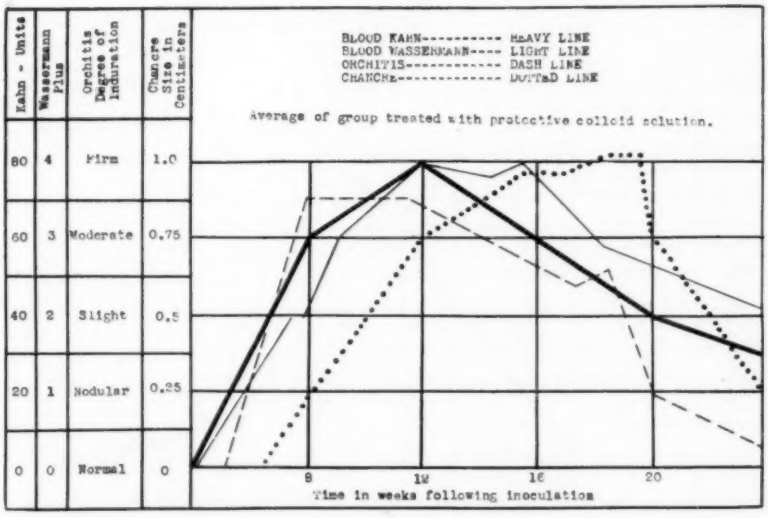

Chart 6.—This group received a total of twelve semiweekly intravenous injections of 7 per cent protective colloid solution in a dosage of 3 cc. per kilogram.

the activity of colloidal mercury sulphide and colloidal copper sulphide in equimolecular proportions (chart 4) is due to its mercury component; colloidal copper sulpharsenite (chart 5) is relatively inactive, and the protective colloid solution (chart 6) shows no activity.

The appearance of signs of active syphilis during the period of latency (which in the rabbit is associated with negative serologic observations) in no instance resulted in the reappearance of a positive Kahn or Wassermann reaction.

A total of 317 paired Kahn and Wassermann tests was performed on 44 rabbits over a period of ten months; in 14 instances (4.4 per cent) comparison between the results of the 2 reactions was impossible because of the anticomplementary action of the serums in the performance of the Wassermann tests. In the 149, or 49 per cent, of the remaining 303 paired reactions, there was complete agreement between the results of the 2 tests. A difference of only 1 plus occurred in 100 of the paired tests. Therefore, in 249 paired tests, or 82 per cent, there was complete or virtual agreement between the 2 reactions. The 54 instances of disagreement (a difference of 2 plus or more) were distributed as follows: 29 showed a difference of 2 plus, 19 a difference of 3 plus and 6 a difference of 4 plus. In 41 of the 54 instances the Wassermann reaction was more positive than the Kahn, and in the remaining 13 the reverse was true. Of the foregoing 41 paired tests, the Wassermann was positive before inoculation in 14.

COMMENT

With increased experience in testing rabbit serums, we have further evidence to support our original method of interpretation of the quantitative Kahn test in experimental syphilis in rabbits; that is, from 0 to 4 unit reactions are interpreted as negative, 20 unit reactions as 1 plus, 40 unit reactions as 2 plus, 60 unit reactions (obtained by interpolation) as 3 plus and 80 unit reactions as 4 plus.

As seen from the results, in only one of the forty rabbits was the Kahn reaction positive (2 plus or more) before inoculation, whereas in five of the animals the Wassermann reaction was positive to one or more tests. These observations do not agree with the results reported in our previous publication, so far as the Wassermann reaction is concerned, as all of the previous series of twenty nonsyphilitic rabbits gave negative reactions to the Wassermann test. It would appear that this variation can be explained only on the basis of a greater sensitivity of the Wassermann reaction used in the second series of tests. Since only one of the rabbits in each of these two series of animals gave a positive reaction to the Kahn test, the Kahn reaction remained a constant. An incongruity that is not explained is the fact that on rechecking two

rabbits that had shown negative reactions to the Wassermann test gave reactions of 3 plus. Both of these rabbits gave negative Kahn reactions on each of the two tests.

In the various groups of animals the Kahn and Wassermann reactions (charts 1 to 6 inclusive and tables 1 and 2) were practically parallel. The relative rates of ascent and descent of the positive Kahn and Wassermann tests are equally divided in the six charts. The time of appearance of equal positive reactions (table 1) and their durations (table 2) were practically the same. These observations are somewhat at variance with our previous impression that there was a tendency for the Kahn reaction to become positive before the Wassermann and to return to negative more slowly when the animal was under treatment. However, in a group of six untreated syphilitic rabbits, the average duration in the Kahn test was 109 days as compared with the duration of 97 days for the Wassermann.

The results corroborate our previous observations of a close parallelism between the serologic behavior and the degree of clinical involvement.

Anticomplementary reactions were found in 4.4 per cent of a total of 317 Wassermann tests. This figure is somewhat less than that previously reported; nevertheless, it is a definite defect of the Wassermann reaction.

The agreement between the Kahn and Wassermann reactions in 82 per cent of 303 paired tests coincides with our previous observations of 83 per cent of 159 tests.

SUMMARY

1. The Kahn test is negative in about 95 per cent of nonsyphilitic rabbits.

2. With the particular technic used the Wassermann test was positive in 12.5 per cent of nonsyphilitic rabbits.

3. There is a definite parallelism between the Kahn and Wassermann reactions and the degree of active syphilitic involvement in rabbits.

4. As the Wassermann reaction shows a high percentage of false positiveness and a definite proportion of anticomplementary reactions, the Kahn test is decidedly superior as a diagnostic agent in experimental syphilis in rabbits.

TREATMENT OF SCABIES WITH THE COMPOUND SOLUTION OF CRESOL*

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Scabies has been a well known disease for many years. As far back as the twelfth century, the Arabian author, Avenzoar, remarked that the "itch" was caused by a small animalcule, but seven centuries elapsed before its cause was actually demonstrated.

About the middle of the sixteenth century, an English physician, Thomas Monfet, again called attention to a small animalcule as the cause of scabies. In 1685, Bonomi, in collaboration with Cestoni, reported the finding of the acarus in the vesicles, calling it *Sarcoptes scabici,* and drew attention to an antiparasitic treatment with sulphur, vitriol, etc., both by baths and by ointments. The treatment continued to be the same, but the causative agent was apparently forgotten—no mention of it was again made until 1812—and even doubted by some illustrious dermatologists, such as Alibert and Biett. About this time, Galès, a pharmacist at the St. Louis Hospital in Paris, reported positive observations in 100 cases, but his organism did not always agree morphologically, and, naturally, much opposition again arose. In 1824, Renucci, a Corsican student, definitely proved its existence and relation to scabies. Renucci, hearing Professor Alibert deny its existence, dramatically extracted a mite from his own skin and demonstrated it to the skeptical professor and assembled students, thus settling a question in debate for seven centuries.

The treatment of choice has always been with sulphur in some form. Sulphur has been an efficient remedy; nevertheless, it has many objections, and search for a substitute has been made by numerous workers. Sulphur ointment or sulphur in combination with other drugs in the treatment for scabies has been "messy," requiring a somewhat prolonged period for a cure and entailing a loss of time from the patient's usual occupation and considerable discomfort from the treatment.

Certain modifications have been tried to curtail the usual length of treatment and avoidance of the sterilization of all clothing. Milian's[1] modification as used in his clinic at the St. Louis Hospital is efficient, but does not avoid the usual "messiness." As Sabouraud remarked, a less "brutal" treatment is needed.

* Submitted for publication, Sept. 25, 1930.

1. Milian: Treatment of Scabies, Brasil-med. **2**:304 (Nov. 17) 1923.

Herxheimer, in 1915, recommended a dusting powder containing 3 per cent tricresol in the treatment for pediculosis.

At the third congress of French-speaking dermatologists held in Brussels in July, 1926, Dekeyser and Minne reported a new form of treatment for scabies, which offered the advantage of being clean, efficient and short, and which avoided the necessity of sterilization of the patient's clothing. This treatment consisted of one or two applications, on consecutive evenings, of a proprietary creolin preparation.

P. Moullard,[2] in 1927, reporting from Ravaut's clinic, confirmed Dekeyser's observations. He strongly advocated the form of treatment used, and remarked that the irritation which sometimes arises is benign and can easily be cleared up by baths or bland applications.

Creolin is defined in Hare's "Practical Therapeutics" as a liquid cresol, a coal-tar product, possessing marked antiseptic but comparatively slight poisonous properties, forming an emulsion up to 12 per cent of the drug.

In the "United States Dispensatory" (edition 21) it is remarked that cresol is only sparingly soluble in water, but is easily dissolved in saponaceous solutions. This is undoubtedly the reason for the proprietary solutions derived from it. There is no reason that any of them should be superior to the official compound solution of cresol, which is as efficacious according to my experience. Cresol ($C_6H_4CH_3OH$) is a mixture of the three isomeric cresols obtained from coal-tar and freed from phenol, hydrocarbon and water; it is colorless, yellowish or pink, of phenol-like odor, darkening on exposure and soluble (1:50) and forms a cloudy solution in water. Liquor cresolis compositus, U. S. P., is 50 per cent cresol brought into clear solution by a potash-linseed soap. It has a phenol coefficient of about 3.

I have used this type of treatment for the last four years, both in private and in dispensary practice, and have found that it in every way fulfils Dekeyser's claims.

In the older type of treatment in which the sulphur ointment and balsam of peru were used, in some cases in combination with beta naphthol, the average number of visits of a patient was 2.23, while with the new treatment this is reduced to an average of 2.2 visits. The age of patients receiving the new treatment varied from 1½ to 50 years. When the older treatment was used, dermatitis was encountered in 3 per cent of the patients, while with the new treatment the incidence is 5 per cent, but the dermatitis is of a mild, transitory type, usually clearing up in two or three days.

The technic of application has considerable effect on the results. For this reason, in dispensary practice it is well to have the treatment

2. Moullard, P.: Thèse de Paris, Presse méd., September, 1927.

applied by a nurse, because if the application is made too rapidly the burning is too intense, and the directions are not followed explicitly. With a piece of cotton held in an artery clamp or forceps, a small area, say the back of one hand, is first covered, enough time being allowed to elapse for the smarting to stop before the application is continued. One must remember that the smarting does not start until the solution has been in contact with the skin for a short period. In this way the whole body, except the neck and face, is treated. The treatment is repeated once or twice, and at the end of a week, if any evidence of further trouble is found, the treatment is again repeated; as a rule, if directions are followed carefully, two treatments thoroughly applied are enough. The same clothing may be worn, but to assure the patient against reinfection it is safer to have the underclothing boiled and the outer clothing steamed or exposed to sunlight as well as ironed.

The advantages of the treatment are that the patient is able to continue his work without having to be smeared with a telltale ointment, and a "messy" treatment is avoided.

LOCAL AMYLOIDOSIS OF THE SKIN*

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Amyloidosis of the internal organs has been thoroughly studied by internists and pathologists for many years, but only in recent times has this degenerative change been recognized in the skin.

In 1905, Pospelow [1] discussed the condition in his textbook. In 1909 Schilder [2] examined the skin of fourteen patients who at post-mortem examination showed general amyloidosis. In seven of the specimens he was able to demonstrate amyloid, even though the skin was normal clinically.

Amyloid is a morphologic, homogeneous, structureless substance, which has peculiar characteristic staining qualities. Methyl violet stains amyloid a metachromatic bright red. Iodine produces a dark brown, and the addition of sulphuric acid changes the brown to a dirty green. The van Gieson method gives a clear yellow.

In examining for amyloid one should test with several stains before making a definite diagnosis, because every example of amyloid possesses a different staining intensity, probably owing to the variation in the age of development. Amyloid of the internal organs is stained in vivo by congo red; unfortunately, in the skin this vital staining method has been unsuccessful. Königstein [3] expressed the belief that this is due to the differences in the blood supply of the internal organs from that of the skin. The congo red test of Bennhold [4] depends on the selectivity of the dye for amyloid in vivo. Ten cubic centimeters of a 1 per cent aqueous solution of congo red is injected intravenously, and after four minutes the dye content of the serum is estimated colorimetrically, for by that time there is a homogeneous mixture of the plasma and the dye. One hour later, the serum is again examined; in the normal serum 19.9 per cent of the dye disappears. If there is present a diffuse generalized amyloidosis, the dye is absorbed by the

* Submitted for publication, Sept. 12, 1930.

* From the Dermatological Clinic, Wilhelminenspital, Vienna, Austria, Professor M. Oppenheim, Director.

1. Pospelow, A.: Lehrbuch die Hautkrankheiten, Moscow, 1905.

2. Schilder, Paul: Ueber die amyloide Entartung der Haut, Frankfurt. Ztschr. f. Path. **3**:782, 1909.

3. Königstein, H.: Arch. f. Dermat. u. Syph. **148**:330, 1925.

4. Bennhold, H.: Kongress d. deutsch. Gesellsch. f. inn. Med., 1922, p. 313.

amyloid, and the loss is much greater up to 60 per cent. This test is of value only in generalized amyloidosis.

Guttmann [5] and Königstein became much interested in the subject of amyloidosis, and besides cutaneous involvement in the generalized form they also described accurately a type of localized amyloidosis of the skin.

Königstein [6] was the first to describe a disseminated eruption in general amyloidosis. He reported two cases, each showing amyloid in the papules that made up the exanthem. It is worthy of emphasis that at autopsy one of the cases showed that the greatest accumulation of amyloid was not in the abdominal viscera, which are the usual depot, but other organs, and even the heavy muscles were involved to a marked degree. The eruption was composed of small papules, varying in size from 0.1 to 0.5 cm. in diameter. Some of the papules were the color of the normal skin, while others were dark brown, almost black. The surface was smooth, flat and shiny, and the outline was spherical. Especially characteristic was the transparency, which was so impressive that one could believe that one was looking at a vesicle. On palpation the papules felt dense and hard. In both of Königstein's cases the exanthem was widely disseminated. In one of the patients the scalp was so infiltrated with amyloid that it felt brittle.

The infiltration apparently comes from the blood vessels. In the subcutis, networks of amyloid casts are formed around the vessels. In the more developed examples, one sees not only strips but masses of amyloid, which are connected with one another. These masses surround and even enclose fat cells. The amyloid deposits do not provoke any tissue reaction in the form of cellular infiltrate or the formation of giant cells. In the cutis the amyloid is found in the epithelial connective tissue spaces. In the deeper layers the deposits are found about the cutaneous appendages. The pressure from below brings about an extreme thinning of the epidermis, and for the same reason the papillary structure is absent in places. Acanthosis and hyperkeratosis are found. The elastica resists the amyloid and persists. To affect the elastica there must be extraordinarily large deposits of amyloid. No cases of generalized amyloidosis with exanthem have been reported except Königstein's two cases.

More numerous, however, are the reports of local amyloidosis of the skin. Guttmann,[5] Juliusberg,[7] Königstein,[3] Freudenthal,[8] Masch-

5. Guttmann, C.: Dermat. Ztschr. **28**:65, 1923.

6. Königstein, H.: Wien. klin. Wchnschr. **14**:157, 1921.

7. Juliusberg, F.: Zur Kenntnis der Amyloidosis der Haut, Dermat. Ztschr. **29**:3, 1923.

8. Freudenthal, F.: Zentralbl. f. Haut und Geschlechtskr. **20**:26, 1926; **27**: 469, 1928; **29**:100, 608 and 768, 1928.

killeisson and Sirkin,[9] Truffi [10] and Jukeliss [11] reported a total of fourteen cases. Kreibich [12] reported a localized deposit of amyloid in a darkly pigmented wart. Lindwurm [13] reported an example of local amyloidosis that could not with certainty be placed in this group, because there were evidences of generalized amyloidosis and because of the location of the deposit. In the report of his case Kennedy [14] raised the question as to whether or not Lindwurm's patient showed any amyloid. The patient had dermatitis atropicans, and the so-called amyloid deposits gave no typical reactions to iodine or iodine and sulphuric acid. Besides this discrepancy, Königstein brought out the fact that in Kennedy's histologic report no special mention was made of the lack of structure and homogeneization of the masses found. Hoffmann [15] suggested that these masses might have been mucinous.

Up to the present no author has attributed to amyloidosis of the skin definite clinical characteristics, so that the condition cannot be established as a morphologic entity. On account of the varied signs and symptoms, all cases differ; however, there are subjective and objective symptoms that are common to all of the cases, and that give the clinician a definite hint of amyloidosis. Before mentioning these symptoms it should be stated that the points are few, probably because of the paucity of the cases reported. No conclusion has been reached as yet as to which sex is the most frequently affected or at what age there is the greatest tendency toward this disease. With the exception of one of Königstein's six cases, in which a 2 year old child was affected, all of the patients were between 20 and 60 years of age. In appearance, the disease remains unchanged for many years. So far as subjective symptoms are concerned, all of the patients complain of terrific itching. The clinical observation suggests the diagnosis of lichen planus or, more often, lichen chronicus simplex (Widal). In all cases, besides the luster and hardness of the nodules, the transparency stands in the foreground. This can be of such a high degree that it might mislead one to think that one is dealing with a vesicle. However, amyloid can be present without this important sign. The transparency depends, on one hand, on the amount of amyloid deposited and, on the other hand, on the relative thickness of the overlying epidermis. The histologic observations are quite uniform. In all cases the amyloid is found deposited in the

9. Maschkilleisson and Sirkin: Acta dermat.-venereol., 1928, no. 10, p. 1079.
10. Truffi, G.: Gior. ital. di. dermat. e sifil. **70**:1, 1929.
11. Jukeliss: Acta dermat.-venereol., 1929, no. 6, p. 663.
12. Kreibich, C.: Arch. f. Dermat. u. Syph. **116**:385, 1913.
13. Lindwurm: Ztschr. f. rationelle Med. **14**:257, 1862.
14. Kennedy, D.: Arch. f. Dermat. u. Syph. **136**:245, 1921.
15. Hoffmann, E.: Arch. f. Dermat. u. Syph. **146**:89, 1924; Deutsch. Dermat. Gesellsch, 1923.

papillae, lying under the epidermis without coming in direct contact with it and being separated from it by a thin layer of connective tissue. Tissue reaction of a high degree is absent in all cases. One sees only here and there a moderate infiltration of cells. The typical change in the epidermis is a hyperkeratotic dyskeratosis. Usually parakeratosis is absent, or present only in a slight degree.

The areas most frequently involved are the extensor surfaces of the extremities. Practically without exception, the skin over a joint is free (both flexor and extensor surfaces are not involved together as a rule), and those areas frequently involved by lichen chronicus simplex, namely, the flexor surfaces, are usually free.

REPORT OF A CASE [16]

History.—A man, aged 65, was admitted to the dermatological ward of the Wilhelminenspital on Jan. 13, 1930, with a history of a condition of the skin that dated back seven years. Three years before admission, there had been a previous entry to the hospital for dermatitis artificialis of the left leg, which resulted from severe itching and consequent scratching by the patient. The inflammation and ulceration present at that time receded under treatment with antiphlogistic packs, followed later by the application of a zinc-gelatin stocking. On his last admission, the patient complained only of severe itching, which was always present. All forms of therapy were without effect and gave only slight relief. The past history showed no previous illness.

Physical Examination.—Examination showed that the skin was normal, except that of the inner and posterior parts of the left calf, where there was an area of 15 by 6 cm. that was pale blue, thickened, tense and of increased turgor. Within this lesion there were numerous yellowish-brown to livid-colored nodules, ranging in size from that of a pinhead to that of a split pea. In the upper portion of the involved area these nodules were definitely separated, but in the lower portion they were closely compressed. However, they were not confluent, and they retained their individual contour. They were slightly elevated, and they had a smooth spherical surface. On palpation these nodules were hard. They had an opaque luster that suggested the phenomenon of transparency.

The Wassermann reaction of the blood was negative. The test with luetin gave negative results. The blood and the urine were normal, as were the results of an internal examination.

A biopsy was made of the central portion of the lesion.

Histologic Examination.—The hemotoxylin eosin stain showed hyperkeratosis of high degree. In some places the rete pegs were longer and wider than normal. The epidermal cells showed no other pathologic changes except a slight swelling. In places the epidermis was thinner than normal, especially above the papillary bodies that contained the amyloid. These papillary bodies were greatly changed, as the normal fibrillary structure had practically disappeared. Instead there were homogeneous masses stained with eosin red; between the masses were cavities and spaces. Wherever the fibrillary structure still persisted and was recognizable, the bundles were thicker than normal and did not have the same regular contour. Just beneath the involved papillary layer the cutis showed some cellular infiltrate.

16. This case was presented and discussed by Professor Oppenheim at the Wiener Dermatological Gesellschaft, March, 1930.

This infiltrate was formed mostly around vessels and consisted of lymphocytes, a few polymorphonuclears and plasma cells. The capillaries were markedly dilated and the endothelium, as well as that of the subpapillary vessels, was swollen. In some of the vessels, the endothelium was lifted from the wall. The walls of the vessel were homogenized in places and infiltrated. Cellular infiltration was also present in the deeper cutis, being noted especially around the vessels and sweat ducts. The van Gieson stain showed that the homogeneous masses that filled the papillary body took a yellow stain. With gentian violet (amyloid) stain, the amyloid masses took a metachromatic red stain. The structureless tissue, called amyloid on account of its staining reaction, filled a number of adjoining papillary bodies. It extended practically up to the epidermis; however, not right up to it. It was everywhere separated from the basal layer by a strip of papillary connective tissue.

Fig. 1.—Showing discrete translucent papules on the posterior aspect of the leg.

If one compares the characteristics of this case with those of the previous reported cases of localized amyloidosis of the skin, it is readily seen that this case is typical of that condition.

COMMENT

The only point left open for question is whether or not there was a general amyloidosis in the case reported. I believe that it can be excluded. Clinically, no signs of such a condition were present. Although suffering seven years from this condition, the patient showed no signs of marasmus and was active for his age and able to work. By this time, a general amyloidosis would have led to more grave clinical signs. Furthermore, the limitation of the amyloid deposits in the papillae indicated a local amyloidosis, which Guttmann called "amyloidosis localis cutis nodularis."

As yet the pathogenesis of the condition has not been definitely determined. The most plausible explanation is that the amyloid is

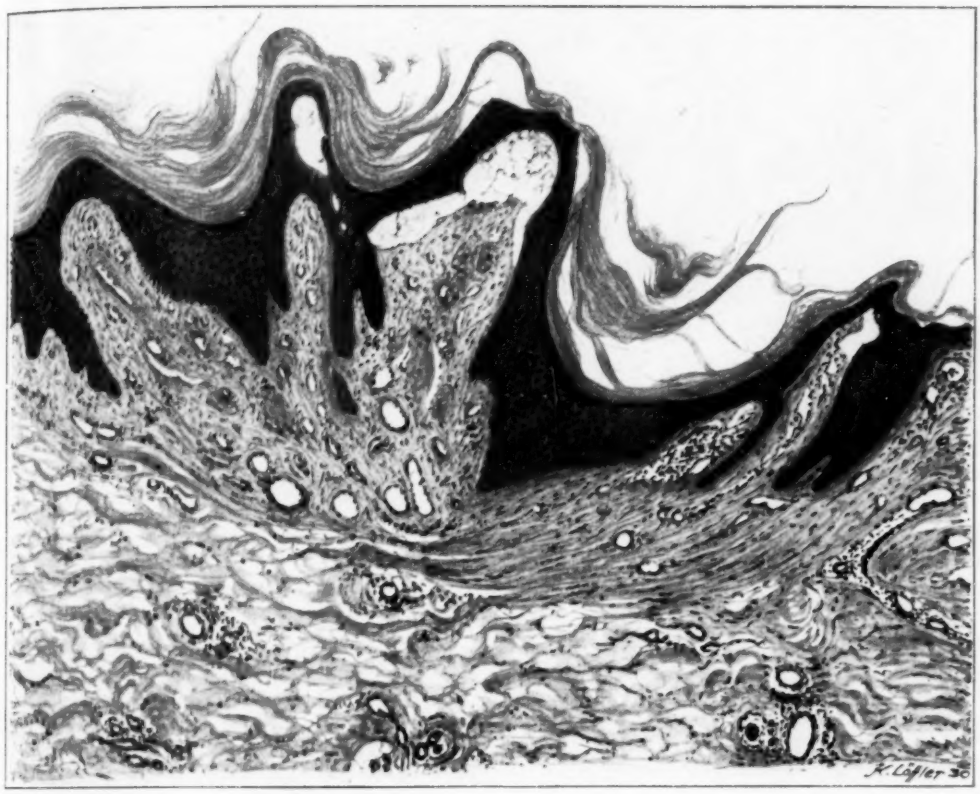

Fig. 2.—Showing hyperkeratosis, slight acanthosis. Homogeneous amyloid deposit about papillary vessels. Vasodilatation and slight infiltrate about the vessels of the cutis. Hemotoxylin eosin stain; × 110.

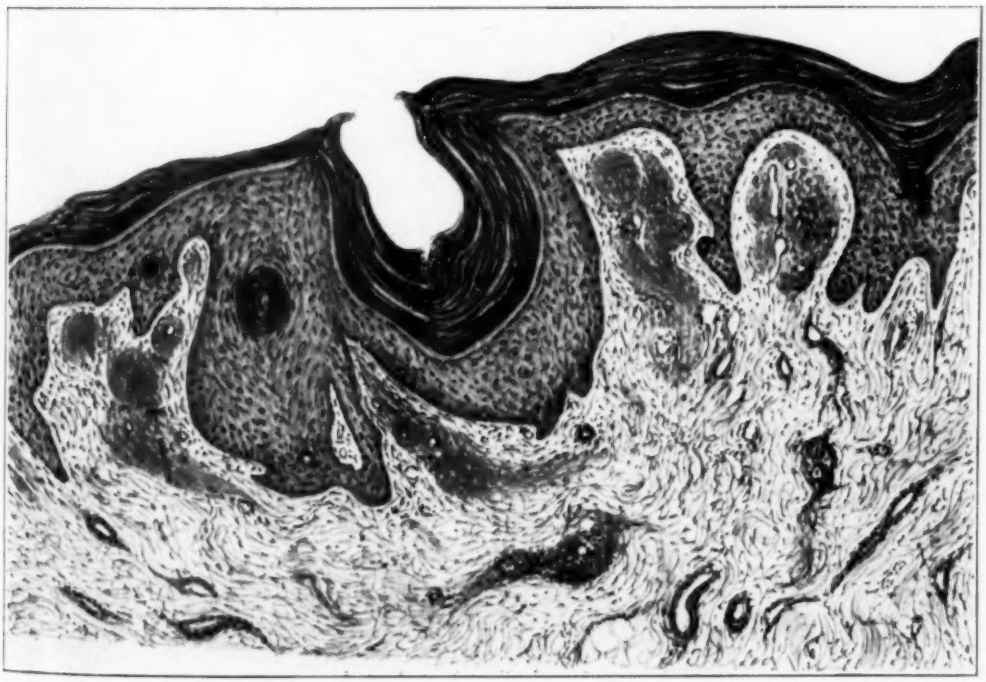

Fig. 3.—Showing amyloid as homogeneous red stained masses in the upper papillary portion of the cutis. Amyloid stain; × 42.

deposited first, and that this is followed by hyperkeratosis of the epidermis. In Königstein's opinion, this does not contradict the fact that in generalized amyloidosis, in which the amyloid deposits are much more massive, hyperkeratosis is not present at times. One can imagine that the hyperkeratosis occurs only in the beginning of the amyloid deposition, and that on progression of the process it disappears. Guttmann did not deny this opinion entirely. In fact he confirmed it by finding that in cases of local amyloidosis there were places in the skin in which amyloid is found without hyperkeratosis. On the other hand, however, in these cases he never found a hyperkeratotic lesion in which there was not a coexisting amyloid beneath the hypertrophic epidermis. Maschkilleisson [17] found amyloid histologically in one case of local amyloidosis in the clinically unchanged skin. He expressed the belief that he had proved that the amyloid deposit is primary, and that the hyperkeratosis is the response to this irritation. However, one must agree with Königstein that in other deposits, such as calcium, there is no hyperkeratosis.

It is important that in local amyloidosis, the amyloid is present only in the papillary bodies. This is the place where the metabolism between cutis and epidermis takes place. In a biologic sense the connective tissue in the papillary bodies is of a different type than that in the rest of the cutis. Changes in this region, either in the metabolism or in the colloidal state, have an effect on the epidermis. Thereby, it can be explained that only deposits of a certain type, those that cause a definite change in the relation of the papillary bodies to the epidermis, such as the amyloid, can lead to the formation of metabolic products that cause the epidermis to become hyperkeratotic. Mechanical deposits, especially the nonorganic type, such as calcium, lack this quality. How the formation of amyloid occurs in this location is as yet unanswered.

No one has formulated an effectual therapy.

SUMMARY

1. A case of local amyloidosis of the skin is reported with typical symptoms of this disease.

2. The condition was of several years' duration and caused severe itching.

3. The typical lesion was a hard, shiny, transparent nodule like those always reported.

4. The amyloid was deposited in the papillary bodies.

5. There was a pure hyperkeratosis without any other peculiarities histologically.

6. There was no evidence of general amyloidosis.

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17. Maschkilleisson: Acta dermat.-venereol. **11**:77, 1930.

TINEA

THE SECOND MOST PREVALENT DISEASE OF THE SKIN *

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The impression has been gaining credence that ringworm infection of the skin has been increasing within the past few years. The increase may now be actual, or cases of tinea may now be diagnosed that in the past were not considered to be due to fungi. It has been interesting to compile the statistics reported from the New York Skin and Cancer Hospital, and their wider publication may be justified.

TABLE 1.—*Compilation of Published Statistics from New York Skin and Cancer Hospital on Number and Percentage of Cases of Eczema, Acne and Tinea*

	Year				
	1925	1926	1927	1928	1929
Total number of patients	21,725	20,244	25,345	27,560	29,145
Eczema	5,565	4,314	4,597	3,520	3,341
Per cent	25	21	18	12	11
Acne	1,877	2,178	2,118	1,859	2,496
Per cent	8	10	8	6	8
Tinea	839	829	1,231	2,140	2,938
Per cent	3	4	4	7	10

TABLE 2.—*Compilation of the Diagnosis of Tinea from the Published Statistics of the New York Skin and Cancer Hospital*

	Year				
	1925	1926	1927	1928	1929
Dysidrosis	93	32	29	13	33
Epidermophytosis	670	266	494	1,828	2,500
Tinea barbae	16	16	21	1	1
Tinea circinata	151	81	113	24	31
Tinea cruris	68	48	74	63	111
Tinea kerion	6	5	16	...	...
Tinea tonsurans	393	289	321	35	62
Tinea unguum	12	3	6	2	2
Tinea versicolor	171	68	131	175	198
Ringworm reported from baby clinic	22	21	26	12	...

Tinea was eighth or ninth in the order of incidence of the most common diseases of the skin from 1913 to 1927, inclusive, which was taken in five-year periods, as explained in my previous compilation.[1]

Epidermophytosis, ringworm of the feet and hands, was almost exactly equivalent to the number of cases of acne for 1928 and 1929.

* Submitted for publication, Oct. 31, 1930.

1. Statistics of the Ten Most Common Skin Diseases, Arch. Dermat. & Syph. **20**:186 (Aug.) 1929.

Routine examinations disclosed some clinical phase of ringworm of the toes in approximately half of the people of postadolescent age in the schools and colleges of the United States, where the disease has been studied intensively since the World War. It will not be so long before ringworm will lead the list of common diseases of the skin, particularly as cases of clinical eczema are studied on the basis of fungi as etiologic factors.

The routine microscopic examination for tinea has not always confirmed the clinical diagnosis. Merely substituting the name "tinea" for the name "eczema" will not aid the clinician in his treatment of the patient.

The use of the intradermal test with trichophytin as a routine may add another diagnostic tool for the differentiation of the infection from the eruption due to tinea. However, the test must be carefully controlled. A series of positive reactions to trichophytin administered intradermally occurred in patients with eruptions clinically pityriasis rosea. It appeared to me that such positive reactions to trichophytin could be interpreted as indicating that the eruption of pityriasis rosea was in the nature of a trichophytid. Microscopic examination, cultivation and transfer tests have not given uniformly positive results for tinea or tinea-like fungi. However, the reactions of a series of patients with acne vulgaris were also positive. This led to the conclusion that the trichophytin used in these cases was at fault. Another possibility was that the patients had cryptic infections with tinea on the toe-nails or in the interspaces of the toes. This study is being continued.

LUPUS ERYTHEMATOSUS

TREATMENT WITH GOLD PREPARATIONS *

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Following Schamberg's introduction of gold sodium thiosulphate in the treatment for lupus erythematosus, several reports appeared on the use of this and similar compounds. For three years these drugs have been widely employed, and it now seems that an attempt to appraise their value in the light of a longer experience would be worth while.

The use of gold compounds in the treatment of patients with lupus erythematosus dates from 1913, when Reute [1] first reported the use of gold potassium cyanide in a case lupus erythematosus. From that time until almost ten years later, little was written on this type of therapy, although in 1917 Adolf Feldt [2] had prepared a new gold compound, 4-amino-2-aurothiophenol carbonic acid, and had been using it with considerable success in the treatment for various types of systemic tuberculosis.

In 1921, Kohrs [3] reported a case of lupus erythematosus with cure by this drug, and in the following year, Martenstein [4] of Breslau reported forty-two cases of lupus erythematosus in which the patients were treated with this compound and in which he had obtained clinical cures in twenty-eight cases and improvement in six. At this time it was being used extensively in various German hospitals and clinics in all types of tuberculous infections; along with many reports of its success, there were three reports of deaths attributed to its use.

In 1924, Rickmann [5] first called attention to the use of the sodium salt of aurothiobenzimidazol carboxylic acid in the successful treatment for tuberculosis of the larynx, but in this country its value in the

* Submitted for publication, Aug. 15, 1930.

* From the Vanderbilt Clinic and the Department of Dermatology, Columbia University, New York.

1. Reute: Deutsche med. Wchnschr. **39**:1727, 1913.

2. Feldt: Berl. klin. Wchnschr. **54**:1111, 1917; Therap. Monatsh. **32**:241, 1918; München. med. Wchnschr. **67**:1500, 1920.

3. Kohrs: Dermat. Wchnschr. **73**:181, 1921.

4. Martenstein, H.: Klin. Wchnschr. **1**:2235, 1922.

5. Rickmann, L.: München. med. Wchnschr. **71**:1609 (Nov. 14) 1924.

treatment for lupus erythematosus was not recognized until some time later. In 1927, Throne, Clark, Van Dyke and Meyers[6] published in the *New York State Journal of Medicine* the results of their experience with it in the treatment for lupus erythematosus.

In the same year that Rickmann brought out this gold salt, Møllgard, in Copenhagen, published a book on "The Chemotherapy of Tuberculosis," in which he reported a long experimental study and a year's clinical experience with a compound of gold and thiosulphuric acid. This substance had been prepared previously by Fordos and Gellis in 1845. Schamberg was apparently the first to employ it in the treatment for lupus erythematosus.

In 1927, Schamberg and Wright[7] reported their work on gold sodium thiosulphate. This paper and that of Throne and his co-workers summarized present knowledge on the treatment with gold compound for lupus erythematosus, and contained full bibliographies of the more important articles related to this subject.

The purpose of this paper is to report my clinical observations during a period of three years in the use of these three gold compounds in the treatment for lupus erythematosus and a few other dermatoses, and to compare the relative values of these drugs in respect to both harmful and beneficial effects.

PATIENTS TREATED

According to Lewandowski's classification, there are but two types of lupus erythematosus, namely: (1) the discoid type, which may be localized or disseminate, and (2) the acute, fulminant type first described by Kaposi in 1872, and more recently brought to attention by George Pernet, who gave this type the name of "le lupus erythemateux aigu d' emblée." The condition, acute in onset, rapid in course and usually fatal, is rarely seen, and I had no case of it.

All of my cases fell within the first group; of these, there were fifty-four of the local discoid type and twelve of the disseminate variety in which there was additional involvement of the neck, back, shoulders, arms and hands. The age of the patients varied between 13 and 75 years, and the lesions of lupus erythematosus had existed for from one month to more than twenty years. Twenty-five of the patients were males and forty-one were females. This ratio is a common observation in this disease.

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6. Throne, Clark, Van Dyke and Meyers: New York State J. Med. **27**:1064, 1927.

7. Schamberg, J. F., and Wright, C. S.: Use of Gold and Sodium Thiosulphate in Treatment of Lupus Erythematosus, Arch. Dermat. & Syph. **15**:119 (Feb.) 1927.

METHOD OF TREATMENT

Before beginning the injections of a gold compound, each patient was given a physical examination, and whenever foci of infection were detected in the teeth, tonsils or sinuses, effort was made to eradicate them before proceeding with further treatment. In a few cases in which the history or examination led me to suspect tuberculous infection of the lungs, roentgenograms were taken to eliminate or confirm this possibility. In every instance urinalysis was made at the beginning of treatment and subsequently at regular intervals during the course of the injections. In only one case was irritation of the kidneys detected, probably due to the gold compound, and this case was one of mild albuminuria, which lasted only two weeks. In more than half of the cases, biopsies were done for study and as a further check against the clinical diagnosis.

During a period of three years, these patients received an approximate total of 690 injections of gold sodium thiosulphate, 290 of 4-amino-2-aurothiophenol carbonic acid and 140 of sodium aurothiobenzimidazol carboxylic acid. At first most of them were treated entirely with the gold-carbonic acid compound, but later, as reports on the efficacy of the other two preparations appeared, the latter were used more extensively. The practice was to continue to treat each patient with one of the gold preparations as long as favorable results were obtained. In cases in which toxic reactions developed or which appeared resistant to one type of preparation, another type was employed, and in some cases all three compounds were used.

When the carbonic acid salt was first used, its lethal possibilities being borne in mind, the treatment was started with a minute dose of 0.001 Gm. This dose was gradually increased until local reactions, such as redness, increased temperature, swelling or some subjective symptom, such as pain or paresthesia, developed at the site of the lesions. When such symptoms appeared, no further injection was given until the reaction had disappeared; this usually took from two to six weeks. A dose of more than 150 mg. was rarely given at one time, although in one resistant and tolerant case, a dose of 350 mg. was employed, which was given every six to eight weeks, without the development of any untoward reaction other than a few small, aphthous ulcers in the mouth.

Injections of gold sodium thiosulphate were given once a week or once every two weeks, and the dose varied between 50 and 500 mg. In spite of the usual tolerance of the patients for this drug, there was no evidence that extremely large doses were more effective than the smaller ones. Because of the increased frequency with which large doses brought about toxic reactions, 100 mg. of the gold sodium thiosulphate, given at weekly intervals, was employed as a routine in the latter part of this three year period, as it seemed to give the optimum results.

With the gold salt of carboxylic acid, the dose varied between 50 and 100 mg., which was administered once a week. Ordinarily 50 mg. was given as a test dose, and in the absence of any unfavorable reaction, 100 mg. was then employed as a routine; in no case was a larger dose given.

As a general rule, patients in whom the lesions were of long duration tolerated the gold compound well, while patients in whom the areas of lupus erythematosus had been present for only a short time or in whom the lesions were disseminate seemed more sensitive to the gold compounds, and in these cases, greater caution in the treatment had to be observed, since in several of them, small doses of the gold compound caused marked irritation of the lesions and the development of new areas of dermatitis which closely simulated lupus erythematosus.

In the cases in which the areas were completely cleared up by the injections, an attempt was made to give at least eight additional injections to insure against further remission of the disease, but the patients did not always cooperate in this prophylactic treatment.

THERAPEUTIC RESULTS

Previous reports on the effect of therapy with a gold compound in lupus erythematosus agree that the majority of patients improve; in general, the reporters have concurred with Schamberg and Wright in noting a virtual clearing up of the disease in about one half of the patients treated, but as the period of observation has so far been short, they have been hesitant in speaking of these patients as cured.

In my series of fifty-six cases of lupus erythematosus, eighteen patients were rendered free from all lesions; nine were markedly improved; twenty-one were moderately improved, and eight apparently were not benefited by the treatment. The cases of ten other patients who received only one or two injections are not included in the series. Most of the patients who were clinically improved showed only a limited number of discoid lesions localized on the face, without involvement of the scalp or the mucous membrane, but it was a striking fact that the duration of the disease, the age of the patient and the number of injections given seemed to have no influence on the prognosis for clinical cure.

The response to treatment of the patients in the first group varied considerably. In one case the condition cleared up after the third injection, but as a rule improvement was slower than this and was noted only after four or five injections had been given. These eighteen patients were followed up for from six months to two years after the last injection, and during that time recurrences developed in two of them, but again the patients were rendered free from lesions by additional injections. In three other cases in which all the areas of eruption had previously been cleared up and in which there had been recurrences the patients were still under treatment for the second time, and therefore these cases were not grouped among the aforementioned eighteen. In the remainder of the cases no new areas of lupus erythematosus developed during this period of observation, but since recurrences can occur, it is perhaps wiser to speak of cases in which the patients remain free from symptoms for a two year period as arrested rather than cured.

The largest group is comprised of the patients who were markedly improved, or only moderately improved, under treatment with a gold compound. There were thirty of them, or 54 per cent of the total series. It was striking to note that in this group improvement was usually evident early in the course of the treatment, but later response became slower or was absent. In some of these cases the condition

seemed resistant to all three gold compounds; in others treatment was stopped before it could be given an adequate trial, while in some toxic manifestations developed that necessitated the cessation of treatment in some cases and a greatly reduced dosage in others.

This group included all except one of the nine cases that showed involvement of the scalp. Under treatment with a gold compound, areas in this region usually improved and became less erythematous and scaly. In the one "arrested" case, the involved area was replaced by a white atrophic scar devoid of hair. In the eight "improved" cases some evidence of activity, indicated by persistent scaliness, dilated capillaries and follicular plugging, remained at the margin of the lesions.

In several of the cases in the group improved by use of the gold compound, residual pathologic changes were finally cleared up through the use of carbon dioxide snow, and in two of the disseminate cases, local applications of 3 per cent tincture of iodine and lotio alba and

Summary of the Results of the Administration of Various Gold Preparations

	Gold Sodium Thiosulphate	Gold-Carboxylic Acid Salt	Gold-Carbonic Acid Salt	Combined	Total
Arrested	11	0	0	7	18
Markedly improved	5	0	0	4	9
Moderately improved	6	1	2	12	21
Unaffected	0	0	3	5	8
Discontinued before the third injection	9	0	1	0	10

the oral administration of 15 grains (0.97 Gm.) of quinine daily seemed to effect additional improvement. Practically no improvement was noted in four cases with involvement of the buccal mucosa, in spite of prolonged treatment in which the doses were raised to the limit of tolerance and all three compounds employed. However, the cutaneous lesions in these same patients were benefited.

The only cases in which no improvement was noted were eight in which the patients proved intolerant to the drug. In these, treatment was discontinued after from the second to the seventeenth injection on account of toxic manifestations which included focal reactions and apparent spreading of the disease. Possibly also some of the ten patients who failed to return after the first or second injection stopped treatment on account of toxic symptoms.

It is generally thought that after injections of a gold compound focal reactions in the lesions are desirable and are followed by improvement, but in this series of cases, attention was brought to this phenomenon less frequently in cases in which the condition was ultimately cleared up than in those that did not respond so favorably.

Possibly the degree of reaction had something to do with subsequent response, and the optimum local effect was often not sufficiently striking

to be brought to attention. However, following some of the most severe local reactions, the lesions became moist and eczematized and showed a tendency to spread; such reactions were not followed by improvement. In some cases of the inflammatory type the apparent extension of the lesions is similar to that which occurs after the use of carbon dioxide, ultraviolet light or other therapeutic agents; this reaction suggests that there are types or stages of lupus erythematosus which at times are difficult to differentiate clinically and in which gold compounds or any other form of active treatment can do only harm. This applied to all but one case with disseminate lesions.

A summary of the results obtained by the various gold preparations in the total series of cases is given in the accompanying table.

RESULTS OBTAINED IN OTHER DERMATOSES

In addition to patients with lupus erythematosus, others with several forms of tuberculosis of the skin and leprosy were treated with injections of the gold compounds. In five cases of lupus vulgaris the patients received between five and twenty-five injections each, with practically negative results.

In three cases of papulonecrotic tuberculids, the patients were given eleven, twenty-one and thirty-three injections of the gold compound, respectively, and in each case, after about six injections, the lesions disappeared and remained absent as long as weekly treatments were continued. However, if the injections were discontinued for a longer period than one month, new tuberculids would appear from time to time.

Almost the same results occurred in seven cases of erythema induratum in which the patient received between two and fifty injections. In one case, the ulcerations and indurated areas disappeared after eleven injections of the carbonic acid salt, except for residual pigmentation, and the patient showed no evidence of recurrence during the next five months while he was under observation. The other six patients showed moderate improvement, but none could be considered cured. Two patients with sarcoids of the Darier-Roussy type each received ten injections of gold sodium thiosulphate, without apparent improvement.

Aside from the cases of lupus erythematosus, one of the most gratifying results was obtained in a man, 28 years of age, who had had numerous lesions of lupus miliaris faciei about the mouth and outer canthi of both eyes for approximately six months. He received sixteen injections of gold sodium thiosulphate, and after the first three injections, improvement progressed steadily to an apparent cure, with only flat pigmented areas persisting where some of the lesions had been previously.

The effect of gold compounds was tried in four cases of leprosy, two of the tuberculous and two of the maculo-anesthetic type. The patients were each given an average of twelve injections of gold sodium thiosulphate, with uniformly negative results.

TOXIC EFFECTS

In this series of cases, particular interest was given to the toxic manifestations brought about by the three gold compounds, and while some of the more transient and less severe manifestations probably were missed, a number were observed in spite of the fact that in most cases the doses of the gold preparations were kept well within what appeared to be safe limits, and each patient was questioned and examined prior to each injection.

Such toxic manifestations are not entirely understood, but numerous theories as to their causation have been advanced. In the days when colloidal preparations of gold were used, protein reactions were frequently seen, but with the new compounds, this factor is eliminated.

Study has shown that gold salts are excreted largely through the kidneys, and therefore may cause serious damage in unfavorable cases. Small quantities are also excreted by the intestinal tract, but evidence of hepatic injury from this cause has not been demonstrated.

Much experimentation has been done to determine the maximum tolerated dose of these compounds for laboratory animals. If the tolerance in animals corresponded to that of man, it would appear that a person of normal size, weighing 60 Kg., could safely be given 2.1 Gm. of gold sodium thiosulphate at a single injection, but such a correspondence cannot, of course, be assumed. In the treatment for lupus erythematosus, the doses were kept far below this amount.

In Germany, several deaths that occurred with signs of renal and meningeal irritation have been reported from the administration of small doses of the carbonic acid salt, while Görl and Voigt [8] reported two cases of severe systemic reaction following the injection of the carboxylic acid compound. The latter were attributed to impurities in the preparation of the compound or to some toxic decomposition product rather than to the gold compound itself. Schamberg expressed the belief that such severe reactions never follow the administration of gold sodium thiosulphate.

In experiments on the toxicity of the carboxylic acid salt, Throne, Clark, Van Dyke and Meyers found that in toxic cases the gold compound acted like the other heavy metals, lead, mercury and arsenic, in causing a reduction in the blood chlorides and an increase in the blood sugar.

8. Görl, L., and Voigt, L.: München. med. Wchnschr. **73**:1360, 1926.

Heubner and Stuhl[9] expressed the belief that the toxic effects of gold compounds were exerted largely on the capillary endothelium, while Adolf Feldt considered that the inflammatory cutaneous phenomena after the injection of the carbonic acid compound were anaphylactoid in origin. They compared the reactions to those following the administration of arsphenamine and tuberculin.

During the course of my observation, seventy-eight individual reactions sufficiently severe to be brought to attention were recorded. Seventy-nine per cent followed injections of gold sodium thiosulphate; 17 per cent occurred after the administration of gold-carbonic acid compound and 4 per cent were the result of injections of the gold-carboxylic acid preparation. The reactions could be grouped under two general headings: (1) those that occurred within twenty-four hours after the injection, and (2) those that occurred after that time.

In two of the cases in which early systemic reactions occurred, rather severe pains developed in the arms and extended from the elbow to the shoulder following the injection. In two patients abdominal cramps developed after the injection of gold sodium thiosulphate, and in one diarrhea. Among the later systemic reactions were rather severe lumbar pains, headaches and pains in the joints. In one case a mild albuminuria developed, and in one a marked glandular enlargement occurred twice following injections. Seventeen of the systemic reactions were due to gold sodium thiosulphate and two to the carbonic acid salt. In the group of immediate skin reactions, there were four cases of acute scarlatiniform erythema which occurred within twenty-four hours after the administration of gold sodium thiosulphate.

Among the cutaneous manifestations of the delayed type were eighteen cases in which erythematosquamous macular eruptions developed, thirteen of which were due to gold sodium thiosulphate, two to the carbonic acid salt and three to the carboxylic acid compound. In eight cases local and generalized pruritus developed following the administration of gold sodium thiosulphate and two after the use of the carbonic acid salt. Six patients complained of rather persistent paresthesias of the palms and soles, which occurred after treatment with gold sodium thiosulphate, and in one the same symptoms developed after the use of carbonic acid salt.

In sixteen cases aphthous ulcers of the mucous membrane of the mouth occurred, of which ten were due to gold sodium thiosulphate and six to the carbonic acid salt. Numerous patients also showed focal reactions in the lesions, but no record was kept of the actual number of cases in which this occurred.

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9. Stuhl, K.: Deutsche med. Wchnschr. **50**:207 (Feb. 15) 1924.

Aside from the four cases in which the acute scarlatiniform type of eruption developed, none of the reactions caused the patients much discomfort. The reactions were easily controlled by discontinuing the injections and administering sodium thiosulphate by mouth and intravenously for a period of two or three weeks. The four patients with the scarlatiniform rash were rather uncomfortable for several days, but they were entirely well in two weeks; associated with the clearing up of the acute eruption, the lesions of lupus erythematosus were much improved.

SUMMARY

In summarizing the data obtained over a period of three years, it seems evident that all three of the gold preparations are of value in the treatment for lupus erythematosus, and they are all superior to any other method so far devised for the treatment for this condition.

Of fifty-six cases of lupus erythematosus, eighteen were arrested and thirty improved. Since in lupus erythematosus recurrences can occur after apparent clinical cure, and since five such cases were observed in the present series, I do not feel justified in saying that patients were cured who remained free from a return of the condition within a period of two years after treatment.

It is interesting to note that although in all of the early cases the patients received only the carbonic acid salt, not one case was arrested by this drug alone. In some cases the condition was cleared up by supplementary treatment with gold sodium thiosulphate or with carbon dioxide snow. However, in disseminated lupus erythematosus of short duration, the carbonic acid salt in small doses seemed to act more favorably than the other two compounds, as in three such cases the other compounds caused irritation and spreading of the lesions.

A satisfactory comparison of the relative value of the three preparations was made somewhat difficult on account of uncontrolled factors, such as the size of the dose, the frequency of administration and the personal equation of every patient treated. However, in spite of this fact, gold sodium thiosulphate was the drug that seemed to give the most consistently beneficial effects, notwithstanding the higher percentage of toxic reactions caused by it.

There were a number of cases in which the areas of lupus erythematosus seemed resistant to all three of the gold compounds. These included all but one of the cases with involvement of the scalp and all of the four cases with lesions of the mucous membranes.

As a precaution against recurrence, patients with "arrested" cases should be advised to take at least eight additional injections of a gold compound during a period of three months following the disappearance of all lesions.

Of the three drugs, 8.9 per cent of the total number of injections of gold sodium thiosulphate were followed by toxic reactions, while 4.4 per cent of the carbonic acid salt and 2.2 per cent of the injections of the carboxylic acid preparation gave similar untoward results, but during the entire period not a single serious reaction occurred. Most of them lasted for only a short while and were easily controlled by discontinuance of the drug and the administration of sodium thiosulphate by mouth and intravenously for two or three weeks.

In the other conditions of the skin for which the patients were treated, this method generally gave disappointing results. In one case of lupus miliaris faciei and in one case of erythema induratum, the condition cleared up and did not recur after further injections were stopped. The other cases showed only transient or no improvement after treatment with the gold compounds.

THE HUMORAL ASPECTS OF IMMUNITY TO SYPHILIS

WITH PARTICULAR REFERENCE TO THE RÔLE OF LIPOIDS AND THE QUESTION OF PRODUCING POSITIVE WASSERMANN REACTIONS IN RABBITS *

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The mechanism of immunity from syphilis is not clearly understood. From the evidence it appears to be more cellular than humoral.

Comprehensive summaries of studies of the immunity to syphilis have been published by Neisser,[1] Levaditi,[2] Bruck [3] and Zinsser [4] and more recently by Chesney [5] and Harrison.[6] A detailed review is not necessary here. A brief summary and a review of recent pertinent experimentations only are given.

Attempts to produce active immunity to syphilis in man or in the lower animals by injecting filtrates of syphilitic tissue, killed and living syphilitic virus and cultures of *Spirochaeta pallida* have generally been unsuccessful.

Attempts at passive immunization with the serum of immune persons or the serum of animals either infected with syphilis or treated with dead cultures of *Spirochaeta pallida* have also proved fruitless.

Comparable to Neisser's studies of passive immunization against syphilis, Bruck [7] gave syphilitic patients an injection of an antiserum obtained from horses inoculated with cultures of *Spirochaeta pallida.*

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* Submitted for publication, Aug. 15, 1930.

* From the Research Institute of Cutaneous Medicine.

1. Neisser, A.: Bericht über die in 1905-1909 ausgeführten Arbeiten zur Erforschung der Syphilis, Arb. a. d. k. Gsndtsamte. **37**:1, 1911.

2. Levaditi, C.: De l'immunité acquise dans la syphilis, Ztschr. f. Immunitätsforsch. u. exper. Therap. **2**:277, 1910.

3. Bruck, C., in Kolle and Wassermann: Handbuch der Pathogenmikroorganismen, Jena, Gustav Fischer, 1913, vol. 7.

4. Zinsser, H.: Infection and Resistance, ed. 3, New York, The Macmillan Company, 1923.

5. Chesney, A.: Immunity in Syphilis, Baltimore, Williams & Wilkins Company, 1927.

6. Harrison, L. W.: Review of Experimental Research in Syphilis and Its Possible Application to Man, Brit. J. Ven. Dis. **5**:173 (July) 1929.

7. Bruck, C.: Beiträg zur Frage einer Serum Therapie bei Syphilis, Klin. Wchnschr. **7**:71, 1928.

This serum was devoid of spirocheticidal action, although it agglutinated *Spirochaeta pallida,* when in dilution up to 1:10,000.

Mulzer,[8] as well as Worms,[9] studied the spirocheticidal activity of antiserum from llamas in experimental syphilis in rabbits, for which Jáureguy and Lancelotti [10] claimed such action. They found it lacking in therapeutic value. Manteufel, Richter and Worms [11] demonstrated the lack of spirocheticidal action of Query's serum in experimental syphilis in rabbits, which was also alleged to possess immune properties.

It appears from the studies of many investigators that there is little status to the immunologic rôle of the antibodies that have been demonstrated in the serum of syphilitic patients or of animals experimentally infected with syphilis.

The reports on the presence of agglutinins in the serum of syphilitic patients are conflicting. Uniform results have been obtained by different workers in the demonstration of agglutinins in the serum of rabbits that have been given injections of cultures of *Spirochaeta pallida.* Curiously, Zinsser, Hopkins and McBurney [12] showed that while cultivated spirochetes were agglutinated, no agglutination occurred with virulent organisms.

Although many experiments failed to demonstrate the spirocheticidal action of the serum of patients with syphilis or of animals infected with syphilis for virulent spirochetes, there are a few studies reported in which such action was demonstrated. In Eberson's [13] investigation, the serum of patients with latent syphilis was mixed with virulent spirochetes and then injected intratesticularly into rabbits. Syphilis did not develop in the animals given injections.

Eberson's results were not confirmed by Manteufel, Richter and Worms [14] nor by Kolmer and Rule.[15] Manteufel, Richter and Worms

8. Mulzer, P.: Zur Serumbehandlung der Syphilis, Klin. Wchnschr. **5**:1920, 1926.

9. Worms, W.: Beiträge zur experimentellen Syphilisforschung, Deutsche med. Wchnschr. **53**:959, 1927.

10. Jáureguy, F., and Lancelotti, L.: Résumé des recherches experimentales sur la syphilis, Bull. Acad. de méd., Paris **92**:1295, 1924.

11. Manteufel, P.; Richter, A., and Worms, W.: Beiträge zur experimentellen Syphilisforschung: Das Syphilisheilserum von Dr. Quéry (Paris), Deutsche med. Wchnschr. **53**:435, 1927.

12. Zinsser, H.; Hopkins, J. G., and McBurney, M. J.: Studies on Treponema Pallidum and Syphilis, J. Exper. Med. **24**:561, 1916.

13. Eberson, F.: Immunity Studies in Experimental Syphilis, Arch. Dermat. & Syph. **4**:490 (June) 1921.

14. Manteufel, P.; Richter, A., and Worms, W.: Beiträge zur experimentellen Syphilisforschung, Arb. a. d. Reichsgsndhtsamte. **57**:297, 1926.

15. Kolmer, J., and Rule, A.: The Spirocheticidal Activity of the Human Syphilitic Serum and the Immunologic Significance of the Wassermann Reaction, Arch. Dermat. & Syph. **20**:90 (July) 1929.

also failed to demonstrate the immune properties of the serum of syphilitic rabbits in different stages of the infection when injected into other syphilitic rabbits. In addition, Kolmer and Rule failed to demonstrate the spirocheticidal action of the serum of patients with syphilis when injected into syphilitic rabbits.

Lack of Spirocheticidal Action in Experimental Syphilis in Rabbits of Serums of Patients in Various Stages of Syphilis

Rabbit (Active Syphiloma of Testes)	Treatment* (Human Serum)	Days Later			Comment
		One	Two	Seven	
112 R.	35 cc.: untreated secondary syphilis plus liver extract from a normal rabbit; Wassermann reaction 4+	Testes swollen four times normal size; dark field: motile spirochetes	.....	.....	Died third day after treatment
105	40 cc.: untreated tertiary syphilis; Wassermann reaction 4+	No gross change; dark field: motile spirochetes	No gross change	No change	No therapeutic result
	Eight days after former treatment, 30 cc.: as result of treatment, Wassermann reaction 4+	No gross change; dark field: motile spirochetes	No gross change	No change	No therapeutic result
107	33 cc.: untreated secondary early syphilis plus liver extract from a normal rabbit; Wassermann reaction 4+	No gross change; dark field: positive	No gross change	No change	No therapeutic result
	Eight days after former treatment, 36 cc.: untreated early syphilis; Wassermann reaction 4+	No gross change; dark field: positive	No gross change; dark field: positive	No change	No therapeutic result
64	30 cc.; treated interstitial keratitis; Wassermann reaction 4+	No gross change; dark field: positive	Dark field; positive	No gross change; lesions larger	No therapeutic result
	Eight days after former treatment, 73 cc. concentrated to 40 cc.: untreated, late secondary syphilis; Wassermann 4+	No gross change; dark field: many more motile spirochetes	Dark field: positive	No gross change; lesions larger	No therapeutic result
77	37 cc.: secondary untreated syphilis from 2 weeks to 6 months	No gross change; dark field: many more motile spirochetes	.....	No gross change	No therapeutic result
148	40 cc.: pregnant women; Wassermann reaction 4+	No gross change; dark field: positive	No gross change; dark field: positive	No change; dark field: positive	No therapeutic result

* The serum was injected intravenously, intramuscularly, intraperitoneally and intratesticularly.

In a study conducted by Cohn,[16] the serum of patients in different stages of syphilis did not agglutinate cultivated spirochetes. Agglutination occurred only after a paralytic subject was given injections of killed spirochetes.

16. Cohn, A.: Ueber Schutzstoffe bei der experimentellen Syphilis, Klin. Wchnschr. **19**:886, 1929.

Agglutination of the spirochetes from a syphiloma in a rabbit by the serum of patients with secondary syphilis was demonstrated by Hauptmann and Gallinek.[17] This serum was studied with and without the addition of an exudate from the lymph nodes of syphilitic rabbits. The addition of the exudate did not appear to influence agglutination. No agglutination was produced by the serum of patients with dementia paralytica. Agglutination was produced with the serum of patients with cerebral syphilis by the employment of cultivated spirochetes.

PURPOSE OF THE EXPERIMENTS AND METHOD EMPLOYED

The purpose of the experiments was to determine the spirocheticidal action of the serum of patients infected with syphilis.

Rabbits with active syphilomas of the testes were given intravenous, intramuscular, intraperitoneal and intratesticular injections of fresh pooled serums obtained from patients with various stages of syphilis. As shown in the accompanying table, the total amount of serum injected at one time varied from 30 to 40 cc. In one rabbit (no. 64), 73 cc. of pooled serum, concentrated by evaporation to 40 cc., was injected. In all but two rabbits, the total quantity of the serum was injected at one time. These two rabbits (nos. 107 and 64) received a second injection eight days after the first. Into one of these rabbits (no. 64), a total of 103 cc. of serum from patients with interstitial keratitis and secondary syphilis was injected.

The serums injected were taken from a pregnant patient and from patients in the following stages of syphilis: untreated secondary, late secondary, tertiary and congenital syphilis with interstitial keratitis.

All of the serums injected yielded a 4 plus Wassermann reaction, except in one experiment (rabbit no. 105). The serum from a patient in the late secondary stage of syphilis, in whom the Wassermann reaction was at first positive, but became negative as the result of treatment, was injected into this rabbit.

After the injection of the serum, the rabbits' syphilomas were observed, and dark-field examinations were conducted in order to note the possible therapeutic results of the injection.

The spirocheticidal activity of human serum from patients in the acute and chronic stages of syphilis was studied according to Eberson's method[13] in the following manner: Two cubic centimeters of human serum was mixed with 0.1 cc. of a suspension of virulent *Spirochaeta pallida*. This suspension was obtained by dividing finely a node from an active syphiloma in the testes of an infected rabbit and mixing it with saline solution. This suspension contained a large number of actively motile *Spirochaeta pallida* per microscopic field. The mixture of spirochetes and serum was placed in a water bath and heated at 37 C. for one and a half hours and was then injected intratesticularly into normal rabbits. In some experiments the mixture was injected unheated. For purposes of control experiments, normal human serum, rabbit serum and saline solution were employed. In these, after the suspension of spirochetes was added, the mixture was injected unheated in some instances and heated in others.

17. Hauptmann, A., and Gallinek, A.: Zur Frage der Schutzstoffe bei Syphilis, Klin. Wchnschr. **8**:1485, 1929.

RESULTS OF EXPERIMENTS

As shown in the accompanying table, serum from patients in various stages of syphilis was devoid of therapeutic effect when injected into syphilitic rabbits. It is to be noted that the amounts employed corresponded to about 600 cc. injected into a patient weighing 60 Kg.

In one experiment (rabbit no. 112) in which serum mixed with liver extract from a normal rabbit was injected, considerable swelling of the syphiloma appeared within twenty-four hours. This swelling was comparable to a Herxheimer reaction. The animal died three days later. The experiment was repeated in another rabbit (no. 107), with negative results.

Mixing serum from patients in various stages of syphilis with virulent spirochetes failed to prevent the infection of rabbits when this mixture was injected intratesticularly. When the animals thus treated, as well as the control animals, were given injections of spirochetes that had not been heated or mixed with serum, syphilis developed after a long period of incubation. This was attributed to the fact that inoculation was made in midsummer, which affects the course of syphilis in rabbits.

The negative results obtained in these experiments correspond with those obtained by most investigators, who failed to demonstrate the spirocheticidal action of the serum of patients with syphilis or of animals experimentally infected with syphilis. These results are in conflict with those obtained by Eberson.

THE POSSIBLE RÔLE OF LIPOIDS IN IMMUNITY FROM SYPHILIS

It appears that there is little direct evidence of a humoral rôle in the defensive mechanism toward syphilis. On the other hand, in a visualization of immunity to infectious diseases generally, it is not entirely reasonable that the mechanism of immunity to syphilis is wholly cellular.

The dictum of Fournier, that patients with pronounced secondary eruptions of syphilis were less likely to suffer later with neurosyphilis, is in line with recent experiments relative to the immunologic value of intracutaneous injections, which emphasize the rôle of the skin as a defensive organ. If the dictum is correct, it is difficult to ascribe the protection of the nervous system solely to the immunity of the tissues.

From available evidence, it seems that the biochemistry of the defensive mechanism in immunity to syphilis concerns lipoids. Increasing knowledge of the rôle that lipoids play in immunity has given a new perspective to that science. From the work of many investigators it appears that lipoids in general, particularly cholesterol and lecithin, have important neutralizing properties against the harmful products

of metabolism and the foreign and toxic material injurious to the organisms.

In regard to the foregoing statements, Suranyi [18] observed cholesterol to be more effective than lecithin. For example, the feeding of cholesterol to rabbits produced a greater immunologic reaction to certain bacteria than did the feeding of lecithin. Injections of cholesterol protected guinea-pigs from a lethal dose of diphtheria toxin. Other investigators have shown that cholesterol protects guinea-pigs from anaphylactic shock.

Landsteiner and Simms,[19] Jermoljewa [20] and others showed that lipoids alone do not act completely as antigens, but that they do so when combined with albumin (hog serum), as they are then capable of producing antibodies.

The true nature of these antibodies in lipoprotein substances has been a matter of much discussion. Much [21] aptly remarked:

> I do not deny the appearance of lipoid antibodies and other antibodies as such. There is of course something in the body which reacts with lipoids after the incorporation of lipoids, but whether they are antibodies in the old sense seems to me questionable. They are "reagene" if one wants a name. It is hardly to be surmised on what they are founded. They certainly cannot be explained on a purely chemical-physical basis. They belong to life, and to all accounts, with the living there always remains a residue never to be grasped. They will never be quite comprehensible. We only see their effects and make use of them for our benefit.

Schumacher,[22] as well as Bergel,[23] studied chemistry of *Spirochaeta pallida* by means of staining. Schumacher concluded that the organism is free from nucleo-acid and, therefore, is poor in oxygen, and that its body is composed, in a large measure, of a gram-negative lipoproteid. Bergel concluded that the organism is of chemically different composition, an outer lipoidal layer and a lipoid, albuminous, deeper layer.

It is perhaps not without significance that Levaditi showed that liver extract mixed with a small amount of bismuth greatly enhances

18. Suranyi, L.: Ueber die Bedeutung der Lipoide für die Biologie und Immunitätslehre, Ztschr. f. Immunitätsforsch. u. exper. Therap. **53**:74, 1927.

19. Landsteiner, K., and Simms, S.: Production of Heterogenetic Antibodies with Mixtures of the Binding Part of the Antigen and Protein, J. Exper. Med. **38**:127, 1923.

20. Jermoljewa, S.: Ueber Antigeneigenschaften der Lipoide, Ztschr. f. Immunitätsforsch. u. exper. Therap. **57**:102, 1928.

21. Much, H.: Ueber Lipoide, Hippokrates **1**:1, 1929.

22. Schumacher, J.: Ueber den chemischen Aufbau der Spirochaeta pallida, Dermat. Wchnschr. **79**:1457, 1494 and 1514, 1924.

23. Bergel, S.: Further Communications on the Biology and Staining of the Syphilis Spirochete, Klin. Wchnschr. **8**:1218, 1929.

its therapeutic activity. Rosen and Krasnow [24] studied the cholesterol content of the blood serum of patients in different stages of syphilis. Their studies show that in early syphilis cholesterol is decreased, and that it increases as the result of treatment or, as the disease progresses, in the absence of treatment.

The theories explaining the physicochemical basis of the Wassermann reaction center around lipoidal substances. One theory is that the reaction is a colloidal reaction between the colloids of the serum and those of the extract. The cause of the alteration is the appearance of products of reaction against the organ lipoids of the host. The original theory that the reaction is the expression of a reaction of an antigen-antibody in the serologic sense has been given recent support through the investigations of Sachs, Klopstock and Weil,[25] Torii,[26] Henning [27] and Brandt, Guth and Müller.[28] These workers obtained positive Wassermann reactions in the serum of rabbits after giving them injections of mixtures of alcoholic extracts of heterologous and homologous organs and hog serum. The results of these studies suggest that an antibody for lipoid is concerned in the mechanism of the Wassermann reaction; whether the lipoid is that of *Spirochaeta pallida* or that of the tissues is controversal. Klopstock [29] expressed the belief that the reaction is antispirochetal lipoid, although he thought that there is a close relationship between the two lipoids. Torii, from his studies, concluded that the reaction more likely concerns antibodies to lipoids of the organs.

Of considerable importance in relation to the rôle that lipoids play in immunity against syphilis is the work of Bergel.[30] This work is concerned with the rôle of fat-splitting ferments in the lymphocytes as

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24. Rosen, I., and Krasnow, F.: Cholesterol Studies in Syphilis, Arch. Dermat. & Syph. **20**:75 (July) 1929.

25. Sachs, H.; Klopstock, A., and Weil, A. J.: Die Enstehung der syphilitischen Blutveränderung, Deutsche med. Wchnschr. **51**:589, 1925. Sachs, H., and Klopstock, A.: Deutsche med. Wchnschr. **52**:650, 1926; **53**:394, 1927.

26. Torii, F.: Ueber den Mechanismus der Entstehung von den syphilitischen Blutveränderungen, Jap. J. Dermat. & Urol. **28**:43, 1928.

27. Henning, L.: Gelingt es bei Meerschweinchen mit Gemischen aus alkoholischen Extrakten arteigener Organe und Schweineserum positive Seroreaktionen, sowie anaphylaktische Lipoid-Antikörper zu erzeugen? Ztschr. f. Immunitätsforsch. u. exper. Therap. **55**:19, 1928.

28. Brandt, R.; Guth, H., and Müller, R.: Zur Erzeugung der positiven Wassermann Reaction durch kombinierte Injektion von Lipoiden und Schweineserum, Klin. Wchnschr. **5**:68, 1926.

29. Klopstock, F.: Ueber die Blutveränderung in Syphilis, Klin. Wchnschr. **7**:1896, 1928.

30. Bergel, S.: Die Syphilis im Lichte neurer experimentellbiologischer und immuntherapeutischer Untersuchungen, Jena, Gustav Fischer, 1925.

a defense reaction against pathogenic organisms containing fat and lipoid antigens, especially the tubercle bacillus and the *Spirochaeta pallida*. He emphasized the rôle of lipoidal substances as a source of the formation of antibodies. He expressed the belief that an important defensive reaction in syphilis is that of the lipolytic enzymes of lymphocacting on the lipoidal *Spirochaeta pallida*. Most of Bergel's conclusions are apparently based on the study of stained preparations.

Bergel [31] gave rabbits injections of lecithin and later infected them with syphilis. The resulting syphiloma persisted a short time, and in other animals it appeared after a long period of incubation, ranging from one and one-half to three months. This, Bergel attributed to the formation of nonspecific antibodies resulting from the preliminary treatment with lecithin.

PURPOSE OF EXPERIMENT AND METHOD EMPLOYED

The purpose of this experiment was to produce positive Wassermann reactions in nonsyphilitic rabbits in order to determine the spirocheticidal activity of such lipoidal antibodies arising from injections of alcoholic extracts or the testicles of normal rabbits plus hog serum, as well as the testicles of syphilitic rabbits. We performed these experiments to determine also the spirocheticidal activity of nonspecific lipoidal antibodies produced by injections of cholesterol and hog serum, and to inoculate the animals thus treated with syphilis.

The following method of Sachs, Klopstock and Weil was employed to produce positive Wassermann reactions in nonsyphilitic rabbits.

An alcoholic extract of a normal rabbit's testicle was made by taking 15 Gm. of the organ and by grinding and mixing it with 75 cc. of a solution of 95 per cent alcohol. This mixture was placed in the incubator for five days and was shaken daily. After evaporating to dryness, the residue was taken up with 75 cc. of a 1:10 saline solution of hog serum. An alcoholic extract of the testes of a syphilitic rabbit containing a large number of motile spirochetes was prepared in the same manner. These two mixtures were injected separately into four normal rabbits; they were given in sixteen intravenous injections in amounts increasing from 1 to 2 cc., at intervals of three and four days. Two normal rabbits were given similar injections of a 1:10 saline solution of hog serum, and two other animals were given injections of the same solution plus a 6 per cent suspension of cholesterol.

To eliminate the frequent occurrence of false positive Wassermann reactions with the serum of normal rabbits, Kolmer's [32] technic, adapted to rabbits' serum, was employed.

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31. Bergel, S.: Die Heilbarkeit der erworbenen Syphilis und die Frage der Immunität, Beihefte z. Med. Klin. (Hft. 6) **25**:115, 1929.

32. The method is described in Kolmer, J. A.: Serum Diagnosis by Complement-Fixation with Special Reference to Syphilis: The Principles, Technique and Clinical Applications, Philadelphia, Lea & Febiger, 1928, p. 347.

The reaction in all animals before injection yielded negative results. The reaction was again registered after six and after sixteen injections. One week after the last injection, all of the animals were inoculated intratesticularly with syphilis. Normal, untreated animals were inoculated as controls.

RESULTS OF EXPERIMENTS

The Wassermann reaction, obtained with Kolmer's technic, remained negative in all of the animals treated. The same animals were successfully inoculated with syphilis, which in no way differed from the infection in the control animals. When the same technic was used, positive Wassermann reactions were obtained only when the infected animals developed active syphilomas.

COMMENT

The negative results are in conflict with the results of others who have produced positive Wassermann reactions by employing the same preliminary treatment, and are apparently in conflict with the experiment of Bergel, who influenced the course of syphilis in rabbits by preliminary treatment with lecithin, which he attributed to the formation of nonspecific antibodies. Cholesterol, rather than lecithin, was employed in our experiments, because Suranyi [18] showed that cholesterol is more effective in producing immune bodies than is lecithin.

It is well known that the serum of normal rabbits, through an unknown cause, frequently yields a positive Wassermann reaction when the test is performed in the ordinary way. We are in accord with the statement of Graetz [33] that the Wassermann test as employed in man is not appropriate for use in rabbits.

The technic of the Wassermann test employed in experiments of the type reported is therefore of considerable importance. The results of such experiments should be considered in relation to the method of the Wassermann test employed.

The investigators quoted in this paper who produced positive Wassermann reactions in rabbits by preliminary treatment such as that employed in the experiments we reported, made no mention of the technic of the Wassermann test that they used. They all mentioned that only rabbits whose serum yielded negative reactions were utilized. In their report, Sachs, Klopstock and Weil [25] pointed out that they were cognizant of the fact that a spontaneous Wassermann reaction is more or less frequent in rabbits. Such an occurrence in their animals was rare, and they endeavored to eliminate nonspecific results by the suitable selection of the extracts and by the careful consideration of all details entering into the question.

33. Graetz: Beiträge zur allgemeinen und speziellen Pathologie der experimentellen Kaninchen-Syphilis, Virchows Arch. f. path. Anat. **254**:382, 1925.

Kolmer,[32] as well as Graetz,[33] adapted the Wassermann reaction to the rabbits' serum, thereby eliminating false positive reactions. Kolmer showed that changing the antigen or the technic changes negative reactions to positive. Heating the serum has considerable influence on nonspecific reactions. Heating the serum to 55 C. for fifteen minutes, as is ordinarily done, increases the likelihood of obtaining false positive reactions.

When employing the method of Kolmer as adapted to rabbits' serum, we have never obtained positive reactions with the serum of a normal rabbit. Positive reactions were obtained only in syphilitic rabbits with lesions in which active, motile spirochetes were present, the reaction becoming negative on their disappearance and positive on their reappearance. Graetz,[33] who employed the technic of which he wrote, had a similar experience.

Henning failed to produce positive Wassermann reactions in guinea-pigs by employing the same preliminary treatment as that used in rabbits. Förtig,[34] Hecht and Schubert,[35] Martin [36] and Frei and Grünmandel [37] failed to produce positive Wassermann reactions in man by similar preliminary treatment, excepting, however, that the antigens were administered intramuscularly. Sachs, Klopstock and Weil questioned the significance of these negative results, since the strength of the antigen injected and the different route of administration deviated from the method that they employed in rabbits.

The technic of the Wassermann test performed in the experiments recorded in this paper, which apparently differed from that employed by others in similar studies, may account for the conflicting results obtained.

The negative results obtained in man and in guinea-pigs and the negative results that we report in this article do not support the hypothesis of the presence of a lipoid antibody in the Wassermann reaction.

1934 Spruce Street.

34. Förtig, H.: Experimentelle Beiträge zur Frage der Erzeugung der syphilitischen Blutveränderung am Menschen und Kaninchen, Ztschr. f. Immunitätsforsch. u. exper. Therap. **52**:328, 1927.

35. Hecht, H., and Schubert, I.: Ueber das Zustandekommen der syphilitischen Blutveränderungen, Deutsche med. Wchnschr. **52**:2151, 1925.

36. Martin, H.: Experimentelle Untersuchungen am Menschen über das Zustandekommen der syphilitischen Serumveränderungen, Dermat. Ztschr. **46**:176, 1926.

37. Frei, W., and Grünmandel, S.: Gelingt es beim Menschen mit Gemischen aus alkoholischem Plazenta-Extrakt und Serum eine positive Wassermannsche Reaktion zu erzeugen? Ztschr. f. Immunitätsforsch. u. exper. Therap. **51**:517, 1927.

INTRAVENOUS VACCINE THERAPY IN STAPHYLOCOCCIC INFECTIONS *

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The therapy described in this paper was suggested by a series of experiments carried out in studying the results of treatment with vaccine in animals made hypersensitive to streptococci in an attempt to find a basis for vaccine therapy in acute rheumatic fever.

These animals were made hypersensitive (allergic) by subcutaneous injection into one area of agar at 45 C. heavily seeded with streptococci. This method of producing and maintaining an allergic state had been demonstrated by Swift.[1] In from twelve to eighteen days after the initial sensitizing dose, the animals were given subcutaneous injections by the method previously used in producing experimental rheumatoid subcutaneous nodules.[2] Into ten places on the right side of the back of each animal was injected subcutaneously $\frac{1}{100}$ of a standard amount of streptococci and into ten places on the left side, $\frac{1}{1.000}$ of the amount. In a former series of experiments with increasing doses, it was found that $\frac{1}{100}$ of the standard amount of streptococci was the smallest amount that would produce subcutaneous nodules in normal rabbits with any degree of frequency, and that with the dose of $\frac{1}{1.000}$ the nodules were seldom produced. It was also found that in hypersensitive animals large nodules would develop from doses too small to have any effect on normal animals. The frequency and size of these multiple subcutaneous nodules were used as indicators for detecting the degree of hypersensitiveness in the animals.

Some of the hypersensitive animals were given an intravenous injection (vaccination) three days before the multiple subcutaneous injections. All of the animals were killed five days after receiving the multiple subcutaneous injections. The character, frequency and size

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1. Swift, H. F.: Reaction of Rabbits to Nonhemolytic Streptococci, J. Exper. Med. **49**:615, 1929.

2. Clawson, B. J.: Experimental Streptococcic Inflammation in Normal, Immune and Hypersensitive Animals, Arch. Path. **9**:1142 (June) 1930.

of the nodules were compared in normal, hypersensitive and vaccinated, hypersensitive animals, and a study was made of the relation of the concentration of the agglutinins in the blood of these animals to the development of the nodules. In table 1 it is observed that the number of multiple subcutaneous injections that produced nodules in the normal animals was small; with the larger doses nodules were produced in 14 per cent and with the smaller doses in 4 per cent. In the hypersensitive animals the number was much larger; with the larger doses nodules were produced in 75 per cent and with the smaller doses in 60 per cent of the animals. In the vaccinated hypersensitive animals, the number was even smaller than that in the normal animals; with the larger doses 10 per cent of the animals showed nodules and with the smaller doses 0.8 per cent. The outstanding difference to be noted between the hypersensitive and the vaccinated hypersensitive animals

TABLE 1.—*Relation of the Development of Subcutaneous Nodules and the Agglutinating Titer in Normal, Hypersensitive and Vaccinated Hypersensitive Animals*

Kind of Animal	Number	Subcutaneous Injections Producing Nodules		Maximum Agglutinating Titer	
		Right Side with Larger Dose, per Cent	Left Side with Smaller Dose, per Cent	At Time of Multiple Injections	When Animals Were Killed
Normal	15	14	4.0	.....	1:200
Hypersensitive	20	75	60.0	1:400	1:400
Vaccinated hypersensitive	12	10	0.8	1:6,400	1:8,000

was the high agglutinating titer in the vaccinated animals. The ratio of the titer between the hypersensitive animals and the vaccinated hypersensitive animals was 1:400 to 1:6,400 at the time of the multiple subcutaneous injections and 1:400 to 1:8,000 when the animals were killed. This sensitizing phenomenon appeared not to be strain-specific, since an intravenous injection of *Streptococcus hemolyticus* desensitized animals that had been made hypersensitive to *Streptococcus viridans*.

These experiments seemed to show that: 1. A localized lesion with destruction of tissue, as in an abscess, tends to make an animal hypersensitive (allergic) to subsequent injections. 2. This local infection stimulates humoral immunity only slightly, as indicated by agglutinins. 3. Further subcutaneous injections do not desensitize the animals, and probably make them more hypersensitive. 4. Animals made hypersensitive to streptococci can be desensitized and new lesions prevented by intravenous administration of vaccine. 5. The vaccinated and desensitized animals differ from the nonvaccinated hypersensitive animals

in that they have a high agglutinating titer. 6. The protective phenomenon is not strain-specific.

With these facts in mind and assuming that the same phenomena attend local lesions due to staphylococcic infection, we applied the intravenous method of vaccine therapy to three patients with chronic infections due to staphylococci.

REPORT OF CASES

CASE 1.—Mary K., a Bohemian girl, aged 15, was admitted to the hospital on Feb. 1, 1930, with an eruption of the skin that had been present for nine years. The condition had been slowly progressing since its onset, and on admission it was more extensive and severe than it had ever been.

When the patient was 6 years of age the eruption had first appeared following chronic osteomyelitis of both tibias. The first lesions developed about the draining sinuses of the legs and subsequently involved the greater portion of both lower and upper extremities, the buttocks and the lower portion of the back. There were also a few lesions on both ears and on the right parietal region of the scalp. The lesions began as superficial vesicles, the contents of which rapidly became pustular. This was followed by involvement of the deeper structures, which caused a painful inflammatory reaction. A majority of the lesions became fluctuant and, if ruptured, exuded a thin, greenish pus. Healing was slow; a low grade inflammatory process persisted for a variable time. A reddish-brown pigmented area remained which slowly became a depigmented scar. In areas subject to irritation, the elbows, knuckles, knees and feet, the healing of the lesions was much slower, and at the site of the infection a raised, papillomatous, violaceous to reddish-brown plaque, having a consistency comparable to that of soft rubber, was formed. These tumors persisted indefinitely, occasionally becoming again the seat of an acute inflammation. New lesions had a tendency to occur in crops, at which time there was general malaise and a rise in temperature to 102 or 104 F. At no time, however, since the onset of the condition, had the patient been entirely free from active lesions.

The patient was underweight. There was generalized adenopathy that was most marked in the inguinal and axillary regions. Physical examination gave otherwise normal results. A roentgenogram of the chest showed no evidence of a pathologic condition of the parenchyma. The Wassermann reaction of the blood was negative. The urine showed the occasional presence of white blood cells, but otherwise nothing abnormal. Blood counts taken at intervals during hospitalization were within normal limits.

Repeated cultures of pus from active lesions showed the presence of *Staphylococcus aureus*. This organism was not agglutinated by the patient's blood serum. Subepidermal inoculations of uninvolved areas of the patient's skin with fresh pus or suspensions of the cultured organism produced an intense urticarial reaction that was followed by the formation of lesions identical in both appearance and course with those already present.

Microscopically, numerous biopsies showed a lesion consisting of a chronic inflammatory process.

There was no history of the ingestion of bromides or other drugs, and a search for blastomycetes gave negative results. The clinical course and symptoms made a diagnosis of vegetative pemphigus or dermatitis herpetiformis untenable. Therefore, a diagnosis of chronic pyoderma was made.

The patient had been under observation in the hospital for five weeks before vaccine therapy was instituted. Treatment had been directed toward building up the general health, together with local antiseptic measures. Some improvement was seen, but new lesions still appeared, and results as a whole were not satisfactory.

Intravenous treatments with vaccine were begun on March 7, suspended cultures of the organism isolated from the lesions being used. The dosages used were

TABLE 2.—*Time and Doses of Vaccine with Temperatures and Agglutinating Titers*

	Date	Dosage of Vaccine	Highest Temperature During Subsequent 12 Hours, F.	Blood Agglutination Titer
Case 1	3/ 7/30	50,000,000	99.0	1:0
	3/11/30	100,000,000	98.8	1:0
	3/15/30	250,000,000	98.8	1:0
	3/20/30	500,000,000	98.6	1:50
	3/25/30	1,000,000,000	98.4	1:100
	3/31/30	1,000,000,000	98.6	1:6,400
	4/ 5/30	1,500,000,000	98.8	1:50,000
	4/10/30	2,500,000,000	99.2	
	4/15/30	2,500,000,000	98.4	
	5/ 1/30	500,000,000	98.6	
	5/ 8/30	2,000,000,000	98.8	1:12,000
	5/14/30	2,500,000,000	98.4	1:12,000
Case 2	3/11/30	50,000,000	98.6	1:0
	3/15/30	100,000,000	98.6	1:400
	3/20/30	1,000,000,000	102.0	1:300
	3/25/30	2,000,000,000	100.4	1:800
	3/31/30	3,500,000,000	100.0	1:6,400
	4/ 5/30	5,000,000,000	101.0	1:1,600
	4/10/30	4,000,000,000	101.5	
	4/24/30	1,000,000,000	101.6	1:12,000
	5/ 1/30	3,000,000,000	102.0	
	5/ 8/30	4,000,000,000	102.2	
	5/14/30	4,000,000,000	102.0	1:6,400
	6/15/30	.....	.....	1:2,500
Case 3	3/15/30	50,000,000	99.2	1:0
	3/20/30	100,000,000	103.0	1:0
	3/25/30	150,000,000	100.2	1:400
	3/31/30	400,000,000	102.8	1:1,600
	4/ 5/30	500,000,000	98.6	1:50,000
	4/10/30	750,000,000	98.0	
	4/24/30	1,000,000,000	98.0	1:12,000
	5/ 1/30	600,000,000	98.6	1:12,000
	5/ 8/30	500,000,000	98.0	
	5/14/30	500,000,000	98.0	1:12,000

increased gradually at intervals of five days. Twelve injections were given with doses ranging from 50,000,000 to 2,500,000,000. The agglutinating titer rose as high as 1: 50,000 (table 2). A majority of the injections caused no demonstrable rise in temperature, and in no instance did this exceed 99.2 F.

The first and second injections were followed by a great increase in the number of new lesions and a lighting up of many of the older dormant lesions. Following the fourth injection, however, there was a definite clinical improvement, as evidenced by rapid subsidence of existing inflammation and the rarity and mildness of new lesions. At the time of the ninth injection, new lesions no longer appeared, and no clinical signs of inflammation existed in the remaining lesions. On May 23, the patient was discharged from the hospital as cured.

CASE 2.—A report of this case of acne conglobata was recently made in the ARCHIVES,[3] to which reference may be made for a more detailed description. Patrick V., an Irishman, aged 45, had had frequent furuncles since early childhood. At puberty severe acne vulgaris developed which persisted through the third decade. He was admitted to the University Hospital on Dec. 14, 1929, for the present condition, which began five years previously. The lesions first appeared on the trunk, but gradually involved other regions, until on admission the eruption had become generalized. The lesions began as deep pustules that enlarged rapidly and became quite painful. Typical lesions became large fluctuating abscesses that ruptured and drained indolently over a long period. Healing of the abscesses was slow and was characterized by the formation of elevated, papillomatous, keratotic plaques. Removal of the cornified layer revealed large, irregular, depressed scars. The appearance of new lesions was frequently accompanied by malaise and a rise in temperature, at times to 104 F.

With the exception of the cutaneous condition, the general physical examination gave negative results. Roentgenologic examination of the chest gave negative results, as did percutaneous and intracutaneous tuberculin tests. Urinalysis and blood counts showed nothing abnormal. The Wassermann reaction of the blood was negative.

Cultures of the discharging lesions showed growths of the staphylococcus which at first was thought to be *Staphylococcus albus.* However, on prolonged incubation the growths invariably assumed a yellow tint. Reinjection of these cultivated organisms into uninvolved areas on the trunk resulted in a duplication of the parent lesion, as did inoculations with fresh pus. The immediate result was a marked urticarial reaction surrounding the site of the injection. Pus obtained from a case of severe indurated acne vulgaris was injected intracutaneously. This resulted in an urticarial reaction which was equal in severity to that caused by the autogenous organism, but which did not produce a pustular lesion. The patient's blood was found to contain no agglutinins for the staphylococcus isolated.

Local therapy, consisting of baths and antiseptic measures, resulted in considerable improvement, and it had been hoped that the patient would progress to a complete cure. However, after a comparatively quiescent period, during which no new lesions developed, a relapse occurred, with the appearance of new lesions and a flaring up of older ones.

Treatments with vaccine were begun on March 11, 1930, after five months of hospitalization. Eleven injections were given with doses ranging from 50,000,000 to 4,000,000,000. The highest agglutinating titer recorded was 1:25,000 (table 2). Although treatment with vaccine was instituted at the time of an exacerbation, prompt improvement was seen, which corresponded fairly closely with the rise in humoral immunity. No new lesions appeared, and there was a rapid decline in the existing inflammatory reactions. However, after eight weeks of treatment the condition was not entirely cured. Two deep-seated abscesses of the buttocks remained and continued to drain, although the rest of the body was entirely free from active lesions. The patient was discharged from the hospital on May 21, but at the time of writing, he was still being followed in the outpatient department.

It seems logical to regard the persistent deep foci in the buttocks as a sensitizing factor that tended to keep this patient in a hypersensitive state. With this

3. Michelson, H. E., and Allen, P. K.: Acne Conglobata, Arch. Dermat. & Syph. **23**:49 (Jan.) 1931.

and the possibility of reinoculation in mind, a radical surgical procedure seems justified, and is to be carried out in the near future.

CASE 3.—Stella H., a somewhat obese married woman, aged 38, entered the hospital on Nov. 18, 1929. For the past seventeen years she had been suffering with ulcerating lesions of the skin that had resisted all of the forms of treatment employed.

At the onset of the condition there appeared over the buttocks and back and in the axillae numerous red, painful, swollen areas, the appearance of which was coincident with a marked pyrexia and prostration. These indurations broke down and discharged pus. The process had been continuous since the onset; the older lesions, after suppurating for a long time, healed with scarring, while new lesions were continuously appearing. The condition had become unusually severe six months before admission. The larger lesions were found in the axillary fossae, on the buttocks and over the symphysis pubis. There were numerous small lesions on the upper part of the back and a few on the arms, thighs and sternal region.

The physical observations were otherwise unimportant. The Wassermann test of the blood and the Pirquet test gave negative results. Urinalyses showed no abnormal observations. On admission, blood counts showed a leukocytosis of 12,000.

Staphylococcus albus was isolated from early unruptured lesions. Biopsy sections from the edge of the ulcer showed a nonspecific inflammatory process. Because of objection on the part of the patient, autoinoculations were not attempted.

Five months of hospitalization and treatment with antiseptic measures produced slow but definite improvement. The lesions of the axillae and buttocks, although reduced in size, continued to discharge, and there was an occasional new lesion in other areas.

Therapy with vaccine was begun on March 15, 1930. Ten injections were given with doses ranging from 50,000,000 to 1,000,000,000. The agglutinating titers ranged from 1 : 50 to 1 : 50,000 (table 2). Improvement rapidly followed. Inflammation and suppuration subsided promptly, and healing quickly occurred. The patient was discharged from the hospital as cured two months after treatment with vaccine was begun. At the time of writing, there had been no recurrences.

The following points of similarity between these patients and the experimental animals suggested that a hypersensitive state (allergy) might be present in the patients, and that they might be desensitized by intravenous vaccination: 1. The possible sensitizing infection occurred in the first case from an osteomyelitis, in the second from repeated attacks of furuncles and in the third from repeated ulcerated lesions of the skin. 2. There was no humoral immunity, as indicated by the presence of agglutinins in the blood of the patients when treatment with vaccine was begun. 3. In two of these patients subcutaneous injections with organisms isolated from the lesions produced lesions the character of which indicated hypersensitiveness to the organisms. 4. Following intravenous vaccinations new lesions ceased to develop, and the old lesions gradually cleared up. 5. Agglutinins in high titers developed in the blood of the patients. The relation of the vaccinated and nonvac-

cinated patients appeared to be comparable to that of the vaccinated and nonvaccinated animals made hypersensitive to streptococci.

SUMMARY

Patients who are hypersensitive to staphylococci, and in whom new lesions frequently develop, may be desensitized by intravenous vaccination and new lesions prevented.

Subcutaneous injections of vaccine not only fail to desensitize, but they apparently stimulate the production of new lesions.

Intravenous rather than subcutaneous vaccination may be indicated against chronic recurrent infections due to staphylococci.

JUVENILE ACRODYNIA

A BRIEF REVIEW OF THE DISEASE AND REPORT OF A CASE SEEN IN NEW YORK *

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Juvenile acrodynia is found in many parts of the world, and has frequently been reported from sections of the United States other than New York City. To date there is but one report of a patient with juvenile acrodynia from this city. The wide publication of a first report usually brings a train of reports of other cases not previously recognized. We believe that there must be many other cases unrecognized and undiagnosed. Since the symptoms are distinctive, there need be no excuse for failure to detect acrodynia. Once seen, the disease leaves an indelible impression on the observer.

Acrodynia, Swift's disease, Feer's disease, pink disease, erythredema and dermatopolyneuritis are a few of the names that have been applied to the disease.

Juvenile acrodynia, while perhaps fairly common, has been widely recognized as a distinct entity only within the last fifteen years. Evers [1] of India, in 1880, described what was probably this malady as "igniped-itis" (intensely burning feet). Swift,[2] of Adelaide, Australia, before the Australian Medical Association, gave the first vivid account of it under the term "erythredema," a name chosen to describe the characteristic changes in the extremities. Clubbe,[3] of Sydney, Australia, applied the descriptive term "pink disease," because of the bright pink color of the hands and feet. Wood [4] also added valuable descriptive cases at this time. In 1920, Feer, of Germany, reported several cases, diagnosing them as a "neurosis of the vegetative nervous system." In 1922, Thursfield and Patterson,[5] of England, cited a case in an infant, aged 11 months, terming it "dermatopolyneuritis." In 1920, Bilderback,[6]

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* From the New York Skin and Cancer Hospital.

1. Evers: Indian M. Gaz., Aug. 2, 1880 (not available).
2. Swift, H.: Lancet **1**:611, 1918.
3. Clubbe, C. F., cited by Wood (reference 4).
4. Wood, A. J.: M. J. Australia **1**:145 (Feb. 19) 1921; abstr., Lancet **1**:811 (April 23) 1921.
5. Thursfield, J. H., and Patterson, D. H.: Proc. Roy. Soc. Med. (Sect. Dis. Child.) **15**:53, 1922.
6. Bilderback, J. B.: Northwest Med. **19**:263 (Oct.) 1920.

of Portland, Ore., reported this disease in the United States in an article on "A Group of Cases of Unknown Etiology and Diagnosis." To Weston,[7] of Columbia, S. C., who did much work in pellagra, is due the credit of first recognizing the symptoms described by Swift six years before. Wyckoff [8] gave the most recent summary of juvenile acrodynia, with twelve case reports. Within the past two years, reports have been made in Toronto, France, Italy, Spain and the Netherlands. Until May, 1929, all reports in the United States had come from the south and the middle and far west. Smith [9] reported a single case from Bellevue Hospital, New York, at this time.

It should be noted that we have omitted in its chronological order the epidemic of adult acrodynia that occurred in France a hundred years ago. Between 1828 and 1830, from 40,000 to 50,000 people, principally adults, were stricken. Chardon, of Paris, used the term acrodynia (painful extremities) in describing the illness. The cause was unknown at the time. It was later thought to be arsenical in origin. Two other epidemics of acrodynia occurred in the nineteenth century, one in Brussels and another in England, affecting a group of beer drinkers. The latter was traced to arsenical poisoning. The similarity of symptoms—erythema, edema and itching of the hands and feet, severe pains in the extremities, gastro-intestinal disturbance and hyperkeratosis—classes these three epidemics together. The century-old acrodynia of adults probably has no relationship to the juvenile acrodynia with which we are dealing at this time. The accident of name alone is common to both.

Undoubted cases of juvenile acrodynia have been observed and reported in India, Australia, Germany, England, France, Holland, Spain, Italy and the United States. The condition is a disease of childhood; the patients are not less than 4 months and not more than 6 years of age. The incidence is greatest in children between 6 months and 3 years. There is no preponderance of one sex over the other. As far as our reviews of the available literature are concerned, the disease has occurred among white children in locations in which both white and colored people are found. In one series of reports about half the cases occurred in December, January and February.

ETIOLOGY

In brief, the proposed etiologic factors for juvenile acrodynia have been: retention of arsenic, dysfunction of the suprarenal glands;

7. Weston, William: Arch. Pediat. **37**:513 (Sept.) 1920.

8. Wyckoff, C. W.: Juvenile Acrodynia, Am. J. Dis. Child. **37**:88 (Jan.) 1929.

9. Smith, C. H.: Tuberculin Skin Reactions, Am. J. Dis. Child. **38**:1137 (Dec.) 1929.

neurosis of the vegetative nervous system, allergy and infection of the upper respiratory tract.

Arsenical poisoning may account for the epidemics in adults in Paris, Brussels and England. There is, however, no supporting etiologic evidence of relationship between arsenical poisoning and the present acrodynia. The suggestion of dysfunction of the suprarenal glands has insufficient proof. Kernoban and Kennedy [10] supported the theory that juvenile acrodynia is the result of a degenerative process of the central and peripheral nervous system. Helmick [11] presented a brief for an allergy as the etiologic factor, but the evidence is indefinite. Van Westreman, Debre and Petot in a report of three cases in Rotterdam, upheld the theory of deficiency in diet, avitaminosis and secondary infection, for they found good, though delayed, results after giving patients a well balanced diet, high in vitamins. McClendon [12] was successful in adding yeast and viosterol to the diet. Perlman [13] reported the complete recovery of a patient placed on a diet high in vitamins, without other treatment. Craig [14] was able to control, but not to cure, the itching and erythema with quartz light; permanent improvement was produced by the administration of a balanced diet and cod liver oil. Zahorsky [15] found treatment of a 9 months old infant with quartz light and tonics ineffective; improvement followed the addition of yeast to the diet. Recovery under this treatment has always been slow, suggesting that dietary deficiency is a secondary rather than a primary cause of juvenile acrodynia.

Byfield,[16] as early as 1920, considered acrodynia as being due to an infection rather than to a dietary disturbance.

In 1922, Vipond [17] isolated a gram-positive diplococcus from the enlarged inguinal node of a patient, and obtained improvement within three days after injecting a vaccine made from this organism. The rapid improvement in cases in which foci of infection in the upper respiratory tract, such as tonsils, adenoids, sinuses or gums, have been cleared up, points to such infections as being the true etiologic factors in juvenile acrodynia.

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10. Kernoban, J. W., and Kennedy, R. L. J.: Acrodynia (So-Called): Study of Pathology, Am. J. Dis. Child. **36**:341 (Aug.) 1928.

11. Helmick, A. G.: Arch. Pediat. **44**:405 (July) 1927.

12. McClendon, S. J.: Yeast and Irradiated Ergosterol in the Treatment of Acrodynia, J. A. M. A. **93**:455 (Aug. 10) 1929.

13. Perlman, H. H.: M. J. & Rec. **130**:370 (Oct. 2) 1929.

14. Craig, R. A.: Arch. Pediat. **44**:581, 1927.

15. Zahorsky, J.: Pink Disease Treated with Yeast, Am. J. Dis. Child. **37**:449 (Feb.) 1929.

16. Byfield, A. H.: A Polyneuritic Syndrome Resembling Pellagra-Acrodynia (?) Seen in Very Young Children, Am. J. Dis. Child. **20**:347 (Nov.) 1920.

17. Vipond, A. E.: Arch. Pediat. **39**:699 (Nov. 19) 1922.

Reports have been found in which juvenile acrodynia was associated with transient symptoms of encephalitis, tonsillitis, bronchitis, conjunctivitis, rhinitis, whooping cough, mental aberration, multiple adenomegaly and gangrene of the fingers. There is no evidence of contagiousness, although more than one member of a family has been affected. Unrecognized and untreated juvenile acrodynia is self-limiting. The symptoms gradually diminish spontaneously, and disappear in from about eight months to a year.

CLINICAL DATA

Differential Diagnosis.—Acrodynia may be distinguished from pellagra, with which it was at first confused, by the absence of a history of pellagragenic diet, by the fading of the red at the wrists and ankles and by the photophobia. It is differentiated practically from measles and scarlet fever by its course, which is not the same as that of the exanthems with which it is confused.

Symptoms.—Four constant symptoms of juvenile acrodynia are: excessive fretfulness, anorexia and loss of weight, erythredema of the extremities and photophobia. There are several other signs and symptoms which, while usual, may or may not appear during an attack. These are listed in their approximate chronological order of onset: history of previous good nutrition and physical development; appearance of characteristic changes after an infection of the upper respiratory tract, with resulting malnutrition and dietetic disturbance; swelling of lymph nodes, principally the inguinal and submaxillary nodes; vasomotor neurosis, as seen in hyperirritability, sleeplessness, paresthesia, photophobia and excessive perspiration; edema of the extremities, which pit but slightly; a fine maculopapular rash, which appears and disappears in irregular inflamed patches of general distribution; erythema, miliaria and desquamation of the hands and feet, accompanied by itching and pain; alopecia; low fever in the early stages of the disease, which may decline when the rash appears; negative results from urinalysis, and a normal blood count, with the exception of a high leukocyte count.

In acute cases, the gums may become swollen, and the teeth may loosen and fall out. The nails are less frequently affected. Cankers and ulcers of the tongue and mouth and of the hands and feet develop because of poor circulation in these parts. The child will bite these irritated spots, and the open sores that result are extremely slow in healing. Blood [18] reported cases in which the flesh of the fingers had been chewed down to the bone and in which gangrene had developed. As the disease progresses, hyperesthesia and finally stupor appear.

18. Blood, Wilke S.: Personal communication.

Prognosis.—The prognosis is good in the recognized cases. Only five deaths have been reported. A fatal result usually is caused by a superimposed infection.

Pathology.—The rarity of deaths from recognized juvenile acrodynia has given few opportunities for autopsies. The reports indicate that degenerative processes of the central and peripheral nervous systems have been found. Chromatolysis has been found in some of the anterior horn cells of the spinal cord, with the cerebral and cerebellar cortex free. Warthin mentioned finding slight changes in the meninges. Examination of the skin has offered nothing of significance.

Treatment.—Treatment depends on the concept of etiology. Those who adhere to the idea of deficiency in food offer evidence of improvement in patients on change of diet. A diet high in vitamins, stressing vitamin B as supplied by yeast, is advocated. Exposure to vital ultraviolet rays is assumed to aid; the symptoms are relieved, although the condition generally is not improved. If food is vomited, forced feeding and repeated offering of food must be resorted to in order to supply sufficient nourishment. Treatment with autogenous vaccine from gland cultures, if this is feasible, offers aid. It is generally accepted that treatment should include food designed to meet the requirements of the patient, but that the greatest help comes from the removal of foci of infection, usually located in the upper respiratory tract. Diseased tonsils and adenoids must be removed immediately, and infection in the gums and sinuses must be cleared up.

REPORT OF A CASE

History.—On Feb. 13, 1930, a boy, aged 3 years, of Polish parentage, was brought to the dermatologic clinic of the New York Skin and Cancer Hospital for itching of the hands and feet, a generalized rash, profuse perspiration and photophobia. These symptoms had appeared during the first week of December, 1929, and had become increasingly severe up to the time of admission. The family history was unimportant, aside from the fact that both parents had occasional colds and bronchitis. The parents and four grandparents were living. The patient was the fourth child, born at full term, with a birth weight of 9½ pounds (4.3 Kg.). He developed rapidly, sitting up at 4 months, showing the first tooth at 4½ months and walking at 12 months. He was breast fed during the first year. The administration of orange juice, alternated with prune and apricot juice, was begun at 8 months. He was not given cod liver oil. At 1 year, the patient received 1 quart of whole raw milk a day, fruits, vegetables and cereals. At 3 years he was taking from 1 to 1½ quarts of whole milk a day, all kinds of meats, fresh fruits and vegetables, salads, cereals, butter, malted milk and candy, but no ice cream. He disliked and refused eggs. He appeared to be well nourished and was above normal weight.

In October, 1928, at 1½ years of age, the patient had bronchitis. In September, 1929, at 2½ years, he had an attack of tonsillitis which lasted three weeks. Two weeks later, the submaxillary glands became swollen and remained so for six weeks, until the first week in December. During these three months, the patient's appetite was poor, his diet consisting of milk, vegetable soup, oranges and tange-

rines; no solid food was taken. In the middle of November, the child became unusually irritable. He spent the entire day lying down and chewing at his hands. During the first week in December, a fine maculopapular erythematous rash, followed by desquamation, appeared on the patient's body and spread to the hands and feet. He commenced to perspire more than usual, to rub his hands and his feet together and to squint at the light. In the middle of December, the illness was diagnosed as scarlet fever, and the child was quarantined. No improvement occurred, and the patient was requarantined for measles by another physician. The appetite continued to be below normal, and the diet was limited to liquids. The symptoms continued to increase in severity. By February, the patient was spending the whole day curled up in bed, burrowing his head into the pillow away from the light and continually whimpering and crying. He never slept more than ten or fifteen minutes at a time; his brothers and sister took turns rubbing his hands and feet, as this alone seemed to relieve the itching and pain. The extremities were edematous and cold to the touch, but perspired profusely. The perspiration at times actually dripped from the fingers and toes. The hair, which had previously been thick, had been pulled out by the child during the past months and was now a mere fuzz. Urination was frequent and movement of the bowels normal.

Physical Examination.—On Feb. 13, 1930, two and one-half months after the first appearance of the rash, the patient was brought to the clinic. He was extremely irritable, whimpered continually, remained in a crouching position and refused to stand erect or to walk. He rubbed his hands and feet together as he sat on the chair. Perspiration was excessive. The body and extremities were covered with a diffuse, fine maculopapular rash. The protuberant parts of the face, that is, the end of the nose, cheeks, tip of the chin, tips of the ears, eyelids, center of the forehead and hands and feet were cold, erythematous, slightly swollen and a bright pink. Photophobia was marked, giving a most unhappy and worried expression to the face.

No fever was present. The urine was amber colored and the results of tests for albumin, sugar and indican were negative. The reaction was acid. Epithelial mucus and amorphous urates were found. Examination of the blood showed: red cells, 4,600,000; white cells, 13,000; hemoglobin, 79 per cent. The differential count showed: polymorphonuclear neutrophils, 52 per cent; lymphocytes, 46 per cent, and transitionals, 2 per cent. No stippling was seen. The results of fluoroscopic examination were negative; no râles were heard, but the breathing was irregular. The tonsils and adenoids were diseased. No masses or tenderness was felt in the abdomen. Reflexes were normal.

Treatment and Clinical Course.—Removal of the tonsils and adenoids was advised. Dressings of a solution of aluminum acetate were ordered for general application. A child's high vitamin diet, stressing fruit and vegetables, was ordered; cod liver oil, 3 drachms (11.2 cc.), and yeast, one-eighth cake, increasing to one-half cake, three times a day, were added; the milk was limited to 1 pint a day.

Two weeks later, although the tonsils and adenoids had not been removed and the diet had been forced, the patient showed slight improvement. He was less irritable, walked when required, but still crouched rather than stood. The rash was fading, but the photophobia was marked. The tonsils and adenoids were removed on March 10. Partial paralysis of the right arm appeared after the operation and lasted for five days. Three days after the tonsillectomy, general improvement was noticeable and advanced rapidly.

The patient was last seen on December 6, when he appeared to be entirely recovered. He was well nourished and had gained weight, although he still

refused meat and eggs. He played with other children every day, was interested in his surroundings, talked freely and slept well. The skin was clear, and the hair was growing. The hands and feet were warm, of normal color and no longer itched.

SUMMARY

1. Juvenile acrodynia is a primary infection of the upper respiratory tract, with accompanying vasomotor neurosis.

2. Further recognition of the condition, detailed study and reports are necessary to determine the true etiology.

SELF-STERILIZATION POWERS OF THE SKIN*

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It is an obvious fact that the surface of the skin has remarkable powers for freeing itself of the constant and ubiquitous organic contaminations by which it is beset. Just how it accomplishes this task and how efficient it really is, remains unknown. These studies were undertaken to help solve these two problems.

Although the broad outlines of these experiments and the ultimate goals to be achieved were conceived before anything was done, no attempt was made to follow a rigid program in the work. Some of the experiments being performed simultaneously were unrelated, except in their broader features, because the subjects were the material that happened to be available in the clinic at the time. It was felt that in the beginning it would be well to obtain as many facts as possible and to utilize these later by relating them in the hope that thereby some fundamental conclusions could be drawn. We were fortunate in striking on a mode of procedure that was simple and that gave quantitative results. Quantitative results have the advantage of reducing the differences of mere qualitative observations, as seen by different persons, and of affording a means of comparison. Just as new experimental methods generally point out the direction in which they may be exploited, it was hoped that the devices that we adopted would suggest their proper use as the work progressed.

An initial control series of studies on normal skin was first made, so as to get a standard of comparison for pathologic skin. An emulsion was made of 1 Gm. of compressed baker's yeast in 100 cc. of water, and 5 cc. of this was diluted in 1 liter of physiologic solution of sodium chloride. An even film of this was spread on a measured area of the skin. The area was divided into four equal parts; the first was then wiped with a swab immediately and the others one at a time at intervals of ten minutes. The material removed by the swabs was planted on maltose agar plates adjusted at p_H 6.0. After incubation for one day

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at 37 C., the number of colonies on the plate was calculated from the average count per square centimeter of several such areas. Besides the yeast organism, a stock culture of *Staphylococcus aureus* (M 23) was used. This was grown on plain agar slants and prepared for spreading on the skin by shaking 5-cc. of physiologic solution of sodium chloride in the growth tube, until it acquired a cloudy appearance. This preliminary emulsion was then diluted in 200 cc. of distilled water and swabbed on the skin in the same way as described for the yeast. The staphylococci were plated on plain agar instead of maltose agar. The curve in chart 1, graph 1, is a composite one; it was constructed from the average values obtained on various areas of the skin and does not exactly represent what takes place on any particular one. But the

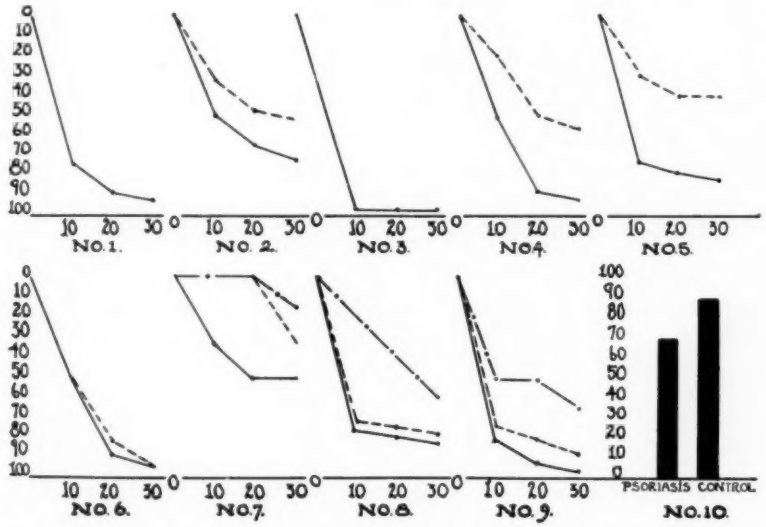

Chart 1.—Graph 1 shows a composite curve for normal persons. In graph 2 the unbroken line represents the values for the skin at the edge of the nail, the broken line for that under the nail. In graph 3 the curve for keratosis is shown. Graph 4 shows the depression in sterilizing capacity in parts of the skin that remain moist because opposing surfaces are approximated. In graph 5 the unbroken line represents the control, and the broken line the denuded, area. In graph 6 the unbroken line represents the values noted before the use of gentian violet, the broken line, those observed after the use of gentian violet. In graph 7, the unbroken line represents the skin used as control, the broken line that under the breast, and the dash-dot line that in the webs of the fingers. In graph 8, the unbroken line represents the control, the broken line the skin in the webs of the fingers and the dash-dot line that under the breast. In graph 9 the unbroken line represents the values for the capacity of the control skin at the end of one interval, the broken line the control at a later interval, and the dash-dot line the control at a still later interval. Graph 10 shows the comparative capacity of skin used as control and that of skin in psoriasis.

difference between one area and another in this group is negligible. So long as the surface of the skin was normally dry, open to the air and intact, little difference was found between one area and an adjacent or even a distant one. Therefore, even though this curve is composite, it would not be inaccurate if it were allowed to represent what takes place at any one area. As can be seen from this curve the greater part of the sterilization is accomplished in the first ten minutes—a little more than 73 per cent. From then on the curve diminishes in steepness progressively, or the total number of organisms removed in each successive ten minutes becomes absolutely and relatively less. The skin becomes less efficient as its task continues. The rate of sterilization at any given period in the experiment can be imagined, for convenience, to be determined by the number of units of sterilizing substance left in the skin after some of them have been removed in destroying organisms plus the increment that is being constantly added to the store while it is being exhausted.

It is curious that the immediate vicinity of the nails should be less efficient than other normal areas of skin (chart 1, graph 2). Perhaps the explanation for this difference is that the nail areas are not normal, strictly speaking. They are situated at points that constantly become traumatized in a greater or lesser degree. As will be shown later, denudation of epithelium is one factor that depresses the skin's sterilization ability. Another possible explanation is the accumulation of dirt about the nails, in support of which Arnold's work may be cited to show that a dirty skin is less efficient than a clean one.

It is easy to imagine that something within the horn cells is responsible for the process of sterilization, and that this entity may be present in a larger total quantity when more horn cells are present. It was therefore thought worth while to investigate the rates for keratotic areas. An examination of them showed, however, that they are not more efficient than normal areas (chart 1, graph 3). In the same way, the palms are not more efficient than the dorsal areas of the hands. The data obtained do not militate against the idea that a substance is contained quantitatively within keratin, and is used also in a quantitative manner. This could still be true if the explanation for the normal readings on the keratotic areas was that only those cells in contact with the organisms, or the uppermost ones, can be of use for sterilization.

Parts of the skin in which folds occur and remain moist because the opposing surfaces are approximated show a decreased capacity for sterilization (chart 1, graph 4). The poorest results were shown under the breasts and perianally. If these areas are allowed to remain exposed to the air for a while, they dry and then show distinct improvement. It has not yet been determined just how long a period of drying is

required for a previously moist area to show the same capacity for sterilization as normal skin. Contrariwise, however, it can be shown that if a dressing of distilled water is placed over an area for twenty minutes it will appreciably depress the values obtained from the area in a previous test. In the same way, moist areas of dermatitis are less efficient than normal areas; this form of dermatitis is but one way in which the surface epithelium suffers from a solution in a continuity; for that reason, it should, perhaps, be included under the next heading. One possible explanation of the changes produced by moisture is the simple one that the agent responsible for sterilization of the skin is water-soluble. Thus, it could be extracted with an aqueous dressing and apparently be replaced by normal processes after an interval.

Partial denudation of epithelium causes an immediate drop in the skin's capacity for sterilization (chart 1, graph 5). Under this heading are included experiments on skins that were exfoliating and the scales of which were of different types and their attachment of varied tenacity. Strictly speaking, it would be proper to include under this heading only those cases in which the epithelium was normal, except for their removal down to varying levels. It was not practical, however, to carry out the experiments under these specifications. Without in any way being conclusive, the experiments seemed to show that poorer results were to be expected as the lower layers of epithelium were exposed. Several areas entirely devoid of epithelium were practically unable to rid themselves of surface organisms. Conclusive results on this point will help to determine the important fact as to whether epithelium is necessary to rid surface tissues of micro-organisms. Therefore, it would be better to elaborate this part of the experiments and to approach it from several angles. It is hoped that this can be done in the future. The implied purpose here is to attempt to show that it is especially the surface epithelium that partakes in the process of sterilization. To that end, areas were chosen that had normal epithelium covering tissue of different kinds and condition. For example, keloidal areas were chosen as well as scars, hemangiomas and young, deep granulomas, such as those in erythema induratum. In all these tests, the results were more or less what one would expect to find normally.

When the ultraviolet rays come in contact with the skin of an animal, they are capable of at least partially supplying certain vitamins in which the animal may be deficient. Many other claims are made for the beneficial action of ultraviolet exposures, most of them, however, unproved. It has become a vogue to give a series of exposures to stimulate resistance to current infections. A series of experiments was performed, therefore, to ascertain whether these rays are capable of reacting on the skin so as to improve its capacity for self-sterilization. Half-

erythema and suberythema doses were administered to normal skin; immediately afterward the exposed areas were tested, and the results compared with those obtained in trials on nonirradiated symmetrical areas. Examination showed that such exposures are incapable of imparting anything to the skin, under the conditions of the experiments, which would imbue it with greater sterilizing abilities (chart 1, graph 6). It is possible that ultraviolet rays are capable of enhancing the sterilizing capacities of pathologic skin, but skin of this kind was not investigated.

Experiments were performed on several persons who were susceptible to yeast infections and who had at least two different forms of these, such as yeast erosions under the breasts, perlèche or erosio interdigitalis saccharomycetica concomitantly or at different times. They were tested over the affected areas and also on normal appearing areas for control purposes. The affected areas showed a depressed capacity for self-sterilization (chart 1, graph 7), but at the same time this capacity in the control areas showed distinct depression, although it was higher than in the pathologic areas. These persons seemed to suffer from a generalized depreciation in the capacity for sterilization of the skin by yeasts, and in certain moist areas, such as in the commissures of the lips, under the breasts and on the finger webs, a still further depression occurred which at times reached a point below the threshold for infection. Almost all of the patients in this group were Russian Jews, who, it is regretted, did not have simultaneous studies made of the blood sugar. It is intended, however, that these studies will be made with parallel estimations of excretions of skin sugar to determine whether the blood sugar and skin surface sugar have any relation to yeast and staphylococcic infections.

Persons with areas of yeast infection, such as erosio interdigitalis saccharomycetica, on one side only were tested over the noninfected symmetrical areas. The average values obtained were decidedly lower than the normal (chart 1, graph 8). It is easy to see, then, that such noninfected areas could become involved, and this helps to explain why conditions like perlèche often tend to be symmetrical.

It is a well known clinical fact that persons who suffer from infections caused by yeast are subject to relapses at intervals. Several such persons were examined for a total of three times at weekly intervals. The initial examination was made over the affected areas during the height of an attack of perlèche or erosio interdigitalis. The results show that such persons apparently undergo cyclic variations in their capacities for sterilization of the affected areas against yeast (chart 1, graph 9).

The results of recent investigations on psoriasis seem to show that yeast organisms bear a relation to this disease. A number of persons with psoriasis, therefore, were selected for examination. Examinations

were made of the lesions themselves as well as of the nonaffected control areas on the same persons at the same time. The average values obtained demonstrated that these persons were distinctly less efficient for the destruction of yeasts over the affected areas as compared with the unaffected control areas (chart 1, graph 10). The results from the latter areas did not differ from the values found in the control series of normal subjects. The values found over the areas of lesions, even though lower than of the normal areas, were better than those obtained from the lesions in the series that included cases of partially denuded epithelium.

A priori, it would be difficult to decide whether lesions of psoriasis with or without scales would give better results. Some of the information already derived would seem to point toward a decrease; on the other hand, other data would lead one to suspect that epithelium that dries out, as do the scales of psoriasis, impairs the sterilizing efficiency of an area that it covers. Therefore, lesions were freed of scales as completely as possible without producing bleeding and tested; the results were compared with those obtained from unaltered lesions examined at the same time and on the same persons. This comparison showed that organisms on scales have a better chance to survive than those on lesions of psoriasis freed from scales (chart 2, graph 11).

A man with psoriasis arthropathique was examined. The lesions were not typical of psoriasis, but were small, closely set pustules, on the trunk and extremities, ranging in size from that of a pinhead to that of a split pea. The secondary lesions were thick, yellowish crusts. The patient's dermatosis was at one time considered to be a dermatitis suppurativa continue of Hallopeau. Repeated cultures from the lesions grew *Staphylococcus aureus* in pure culture. Cultures of this organism were prepared as emulsions in the way already described and used several times to test the patient's ability to remove them from his skin. At the same time the unaffected areas and those with lesions were examined for their actions on yeast. These tests showed that the patient's skin was totally unable to remove the yeast used or the staphylococcus found in the lesions. The total number of organisms planted on the skin at the beginning of the experiments could be recovered at the end of them (chart 2, graph 12).

From the work of Churchman and the reports of other authors, it has become known that yeasts are vulnerable to gentian violet. Patients with psoriasis were given intravenously 10 cc. of a 1 per cent aqueous solution of gentian violet and were tested before and afterward with yeast emulsion. In each instance, the values previously obtained over psoriatic lesions were appreciably improved thirty minutes after the administration of gentian violet (chart 2, graph 13).

Intravenously administered gentian violet had little effect on the curve of the control, noninvolved areas in psoriasis (chart 2, graphs 14 and 15). The curve here was as good as that for normal skin, so that little change for the better was to be expected.

Whether gentian violet has the effect of modifying the action of the normal sterilizing principles within the skin or whether it superimposes its own action on that usually present in the skin could not be deduced from these experiments. If a modification of the usual agents

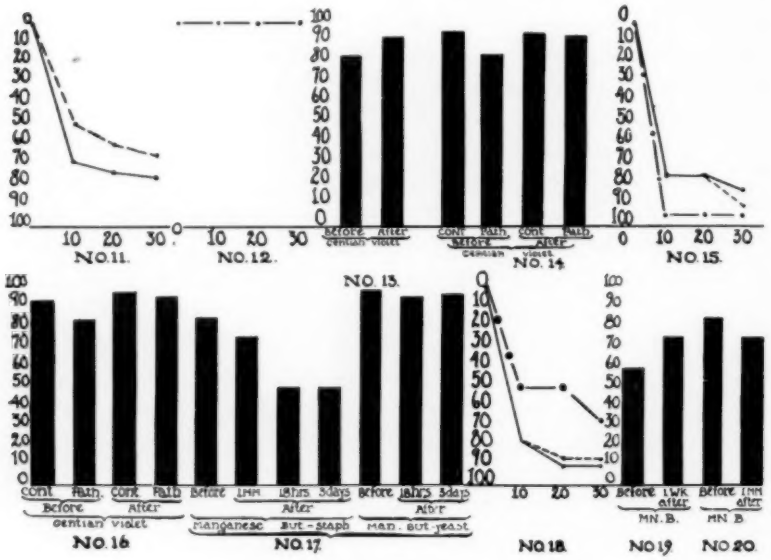

Chart 2.—In graph 11, the unbroken line represents the self-sterilizing capacity of psoriatic lesions after the avulsion of scales, and the broken line the capacity of the skin before the avulsion of scales. Graph 12 shows the incapacity of the skin in psoriasis arthropathique to rid itself of organisms. Graph 13 shows the appreciable improvement in the values obtained from skin with psoriatic lesions after the use of gentian violet. In graphs 14 and 15 it is noted that gentian violet has little effect on the curve for the control, the noninvolved, area in psoriasis. In graph 15, the unbroken line represents the values found in furunculosis before the administration of manganese butyrate, the unbroken line those noted one-half hour later, and the dash-dot line those noted one day afterward. Graph 16 shows that greater efficiency produced by the intravenous use of gentian violet required a certain interval of exposure of the organisms. Graph 17 shows the comparative values obtained in furunculosis, before and after the use of manganese butyrate. In graph 18 the unbroken line shows the values in furunculosis before, the broken line one-half hour after, and the dash-dot line one day after the intramuscular injection of a solution of manganese butyrate. Graph 19 shows the rise in sterilizing capacity after the second administration of manganese butyrate. In graph 20, it is shown that pain is not a factor in the effect of manganese butyrate on the sterilization curve, since pain, which was felt one-half hour after the injections, had no effect on the curve.

for sterilizing the skin is induced by gentian violet, some similar action should be obtained in the intact skin, too. However, this was not demonstrated, as stated in the last paragraph. Its effect on the organisms over psoriatic areas began to appear later in each experiment. There was a preliminary phase during which the rate of destruction of organisms was the same as that found without the use of gentian violet; this phase was succeeded by one that was distinctly stronger than the corresponding part of the curve for the same lesion before gentian violet was used. The greater efficiency derived from the intravenous use of gentian violet required, then, a certain interval of exposure of the organisms (chart 2, graph 16 and table).

An epithelial barrier between the surface and the humoral interior should logically tend to keep outside what is out; contrariwise, it should keep inside what is in. Accordingly, a normal epithelial covering should tend to minimize the influence of antiseptics within the blood on organisms on the skin's surface. The results of some of these experiments can be interpreted so as to confirm this reasoning. Although an antiseptic influence of the intravascularly administered gentian violet could not be shown on the normal, control areas, it was found over the areas occupied by psoriatic lesions. This was an improvement in the values found for the same lesions before gentian violet was used. It may be that the peculiar proximity of the papillary, capillary bed to the surface found in psoriasis bears some relation to these results.

Furunculosis is caused by the pathogenic activity of *Staphylococcus aureus* at the site of hair follicles and lends itself to investigation by these experiments. Even if the simple, narrow view is avoided that growth of the organism to the exclusion of the host's complex reactions determines infection, it might, perhaps rightfully, be suspected that the skin's sterilizing power for staphylococci is impaired in furunculosis. The result of several of these experiments showed that the skin was definitely less efficient against *Staphylococcus aureus* in chronic furunculosis than it was normally. Areas situated near, but not including, the inflammatory zone of furuncles were selected for the tests. At the same time smaller areas were examined for their action against yeast emulsion. The result of these examinations showed that in furunculosis, although yeasts are removed at about the same rate that they are on normal skins, staphylococci enjoy a certain degree of immunity (chart 2, graph 17, values obtained before the use of manganese butyrate).

At the present time, certain of the metallic elements have a widespread vogue in the treatment for furunculosis. The clinical trial of manganese butyrate in furunculosis was made even before these experiments began, and seemed to exert a beneficial effect in at least some of the cases in which it was tried. The sterilizing powers exerted

against staphylococci early in the experiment were depressed directly after 1 cc. of a 1 per cent aqueous solution of manganese butyrate was injected intramuscularly (chart 2, graphs 17 and 18). But at the same time that manganese butyrate enabled greater numbers of staphylococci to survive, it had no effect on yeast. Of course, the rate for sterilization against yeast in these patients with furunculosis was already as high as that for normal skin, so that but slight increase could really be expected from the use of manganese butyrate. However, the fact that this rate was high gave all the more opportunity for decreases to become evident. This, however, did not occur. These results would seem to be evidence that the principles of sterilization for different organisms on the skin are not the same. If staphylococci are partially immune to destruction on the skin of a person with furunculosis and yeasts are not likewise immune, it would seem that there are multiple, if not specific, agents to combat micro-organisms on the skin. It would be interesting to examine persons susceptible to infection with yeast who are given manganese butyrate therapy.

It was not possible to repeat the tests daily for an entire week on the same person; several of the patients, however, were examined daily for as long as four days from the time manganese butyrate was administered. During this period the depression became progressive for the first three days and remained stationary for the next, or fourth day. The basic principle of nonspecific therapy, which rests on complex forces, is an initiation of a change in physical equilibrium. Its purpose is to begin a cycle. This cycle usually begins in the form of a depression, and rolls on to a later period of elevation. The repetitions in the therapy are so spaced as to make the most of the cyclic amplitude peculiar to the substance used.

A series of experiments was conducted to study the effect of manganese butyrate given at an interval of a week. A series of two such injections was given to each patient. It is impossible to say whether the extreme depression found on the third and fourth day ran parallel to the period of greatest concentration of the metal in the blood stream, but it is conceivable that this might have been the case. In these tests it was found that the skin was more efficient against staphylococci one week after the use of manganese butyrate than it was at the time of its use. Immediately after this week's interval the manganese butyrate was again given. A depression ensued, just as after the first injection. But even though the second dose was one and one-half times that of the first one, the lowest point of the depression after the second was not as low as that after the first. After the second injection a similar rise was again found a week later, which paralleled the rise one week after the first, and brought the sterilization powers of the skin to a new high level (chart 2, graph 19).

Average Values for Items Shown in the Curves

Area and Condition	Graph, No.	No. of Cases	Cell Count				Removal, per Cent		
			Control	10 Min.	20 Min.	30 Min.	10 Min.	20 Min.	30 Min.
Normal skin	1 and 5	30	7,364	2,000	883	515	73	88	93
Normal nasal mucosa	..	10	1,160	353	220	90	70	81	92
Edge of nail	2	5	6,000	3,000	2,000	1,500	50	67	75
Under nail	2	5	6,000	4,000	3,500	3,000	33	49	51
Keratotic areas	3	4	3,000	480	420	360	98	98	98
Control dry areas on those with moist areas	4	10	6,000	3,000	720	420	50	88	93
Moist folds	4	10	6,000	4,800	3,000	2,400	20	50	60
Exfoliating dermatoses	5	2	6,000	4,200	3,600	3,600	30	40	40
Before ultraviolet rays	6	2	600	300	80	25	50	87	96
After ultraviolet rays	6	2	4,200	2,100	600	150	50	86	96
Control areas on those susceptible to yeast infections	7	8	6,000	4,000	3,000	3,000	34	50	50
Beneath breasts of those susceptible to yeast	7	7	6,000	6,000	6,000	4,000	0	0	34
Finger webs of those susceptible to yeast	7	8	6,000	6,000	6,000	5,000	0	0	18
Control area indifferent for those susceptible to yeast	8	6	3,000	720	600	360	76	80	88
Unaffected symmetrical area in erosio interdigitalis saccharomycetica	8	6	3,000	720	720	600	76	76	80
Unaffected symmetrical area of erosion under breast (yeast)	8	5	3,000	.....	1,800	1,200	..	40	60
Psoriatic lesions before gentian violet	13, 14 & 15	5	6,000	1,500	1,500	1,000	75	75	83
Psoriatic lesions after gentian violet	13, 14 & 15	5	6,000	1,500	1,500	700	75	75	91
Psoriasis, control area before gentian violet	14 & 15	5	6,000	300	300	300	95	95	95
Psoriasis, control area after gentian violet	14 & 15	5	6,000	300	300	300	95	95	95
Psoriatic lesions before gentian violet	16	3	1,800	360	360	300	80	80	84
Psoriatic lesions after gentian violet	16	3	4,500	900	900	130	80	80	97
Psoriasis, control areas before gentian violet	16	3	4,200	1,260	500	240	70	80	94
Psoriasis, control areas after gentian violet	16	3	4,000	600	30	30	85	99	99
Furunculosis before manganese butyrate: staphylococci	17 & 18	8	5,400	1,800	1,200	1,020	67	78	83
Furunculosis, ½ hour after manganese butyrate: staphylococci	17 & 18	8	2,700	1,200	1,200	720	55	55	75
Furunculosis, 18 hours after manganese butyrate: staphylococci	17 & 18	8	4,800	3,000	2,400	2,400	38	50	50
Furunculosis, 3 days after manganese butyrate: staphylococci	17 & 18	4	6,000	4,500	3,000	3,000	25	50	50
Furunculosis before manganese butyrate: yeast	17 & 18	8	3,300	180	50	10	94	98	99
Furunculosis, 18 hours after manganese butyrate: yeast	17 & 18	8	4,800	600	300	300	87	94	94
Furunculosis, 3 days after manganese butyrate: yeast	17 & 18	4	6,000	1,200	300	300	80	95	95
Furunculosis, before second dose of manganese butyrate: staphylococci	18	3	2,400	600	240	240	75	90	90
Furunculosis, ½ hour after second dose of manganese butyrate: staphylococci	18	3	2,400	600	300	300	75	88	88
Furunculosis, 1 day after second dose of manganese butyrate: staphylococci	18	3	1,800	900	900	600	50	50	68
Yeast-affected areas, first week	9	4	6,000	3,000	3,000	2,000	50	50	67
Yeast-affected areas, second week	9	4	3,000	720	600	360	76	80	88
Yeast-affected areas, third week	9	4	900	180	18	8	80	92	98
Psoriasis, control areas	10	6	6,000	420	240	180	93	96	97
Psoriatic lesions	10	6	6,000	3,000	1,800	1,800	50	70	70
Psoriatic lesions with scales	11	3	6,000	3,000	2,400	2,000	50	60	67
Psoriatic lesions without scales	11	3	6,000	2,000	1,800	1,500	67	70	75
Psoriasis arthropathique	12	1	12,000	12,000	12,000	12,000	0	0	0
Psoriasis, before manganese butyrate: staphylococci	19	3	1,260	720	720	480	40	40	60
Psoriasis, after manganese butyrate: staphylococci	19	3	2,700	1,200	1,200	720	55	55	75
Furunculosis, before manganese butyrate: staphylococci	20	8	5,400	1,800	1,200	1,020	67	78	83
Furunculosis, after manganese butyrate: staphylococci	20	8	2,700	1,200	1,200	720	55	55	75

The intramuscular injection of manganese butyrate produces local pain, which varies in degree in different persons and lasts for about two or three days. It might occur to some that the nonspecific effects induced by manganese butyrate could possibly be reflexly accomplished by some means that began with the sensory nerves. It is known, for instance, that just such sensory reflexes can determine the caliber of distantly removed capillaries. It is felt that the results of these tests can be used to show that pain is not a factor in the effect of manganese butyrate on the sterilization curve. The pain had already begun to be felt one-half hour after the injections, and yet no great change had been registered in the curve (chart 2, graph 20).

The accompanying table gives the average values for the items used in the curves. It contains the average values on which the various interpretations expressed were based. It was felt that its preparation in this form would prevent the confusion caused by an intermingling of figures with text.

SUMMARY

1. Yeast cells are removed from the surface of the skin at an almost uniform rate that varies little from one area to another as long as the surface epithelium is normally dry and intact.

2. The nail beds and areas immediately surrounding the nails are less efficient at sterilizing themselves than are other normal areas.

3. Keratotic areas are no more efficient at removing yeasts and staphylococci from their surfaces than are normal areas.

4. Moist areas suffer a depression of their sterilizing powers.

5. Areas with denuded epithelium are not as efficient in removing yeasts and staphylococci as intact ones.

6. Previous exposures of the intact skin to ultraviolet light do not enhance its destructive powers against yeasts and staphylococci.

7. Areas superficially infected with yeast, such as those of perlèche, are barely capable of destroying yeasts.

8. The unaffected areas symmetrical to those superficially infected are distinctly lower in their sterilizing powers against yeasts than the normal areas, although higher than the affected ones.

9. Persons susceptible to infections with yeast vary in their yeast-sterilizing rates from time to time, and this variation appears to be somewhat periodic.

10. Areas occupied by psoriatic lesions suffer from a loss of sterilizing powers as compared with uninvolved areas on the same persons.

11. Psoriatic lesions bared of scales free themselves of surface yeast and staphylococci more quickly than do such lesions with scales.

12. In a man with psoriasis arthropathique, the sterilizing powers of the skin were found to be entirely lacking against yeasts and staphylococci.

13. Gentian violet administered intravenously augments the sterilizing powers of the skin over psoriatic lesions for yeast.

14. Gentian violet administered intravenously has little effect on the rate of destruction of yeast over normal areas.

15. A certain latent period of contact with the skin is required before the intravenously administered gentian violet shows its effect in the curve for destruction of yeast.

16. Staphylococci remain on the skin of persons with furunculosis longer than on that of others; yeasts, however, are removed just as quickly in those with furunculosis as in normal persons.

17. Intramuscular injections of manganese butyrate almost immediately depress the skin's rate of destruction of staphylococci, but do not alter that for yeasts.

18. One week following an injection of manganese butyrate, the rate of sterilization for staphylococci is greater than that just before the injection.

19. The changed rate of sterilization produced by manganese butyrate is not through the medium of sensory nervous paths leading from the site of the local pain that results from the injections.

THE STRUCTURE OF THE JUNCTION OF THE EPIDERMIS AND THE CORIUM *

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The view of histologists concerning the structure of the junction of the epidermis and the corium has undergone essential changes with time, especially since precise knowledge of the so-called argyrophil lattice fibrils or argyrophil reticulum was obtained.

As is well known, investigation was first made of the behavior and structure of the basement membrane described by Todd and Bowman. By employing the newest methods, histologists succeeded in demonstrating the finest elements of the basal layer and of the connective tissue of the papillae. Herxheimer [1] changed his former belief in the existence of some membrane, emphasizing its origin from the connective tissue; at the same time he pointed out that fine fibrils proceed from the basement membrane into the basal layer and that the basal cells also have fibrils reaching the membrane. As is now well known, this connection is reciprocal. As early as 1895, Nékám [2] called attention to the fine elastic fibrils of the papillae reaching the basal layer. Recently Homma, Welti, Frieboes and Kogoj also discussed the condition of the junction of epidermis and corium. Particularly since knowledge of the argyrophil fibrils was obtained, it seems as though it would not be necessary to assume the existence of a basement membrane. According to the opinion of modern investigators, the membrane-like histologic formations chiefly obtained from edemic and acanthotic epithelium, particularly on the lower surface of the epithelial papillae, are secondary elements formed during the proliferation of the epithelium. In reality they consist of compressed collagen fibers.

In the course of the present investigations, employing the Herxheimer-Lugol method, no membrane-like element could be found on the top of the papillae. In silver-impregnated preparations I was able to observe the splitting of this membrane into fine fibrils in the sides of the papillae.

In the formation of the junction of the epidermis and corium two elements are of importance: the processes of the epithelium cells passing

* Submitted for publication, Sept. 18, 1930.

* From the Dermatological Clinic of the Royal University of Budapest, Prof. L. A. Nékám, Director.

1. Herxheimer: Ueber die epidermidale Basalmembran, Dermat. Ztschr. **23**: 129, 1916.

2. Nékám: Quelques considérations sur la disposition et la fonction des fibres élastiques de la peau, Ann. de dermat. et syph. **26**:109, 1895.

to the connective tissue of the papillae and the silver-impregnated fine lattice fibrils of the subepithelial layer. The fine elastic tissue of the papillae also plays a rôle. In this paper I shall deal with the aforementioned three elements.

For examination of the connective tissue there is an elective method at one's disposal: Bielschowsky-Maresch silver impregnation. This method reveals the finest fibrils of the connective tissue and surpasses other methods employed for the same purpose. On the basis of this method, Homma [3] first demonstrated, in 1922, the great importance of the subepithelial lattice fibrils in the formation of the junction of

Fig. 1.—Subepithelial lattice fibrils in normal skin of the axilla. Bielschowsky-Maresch silver impregnation.

the epidermis and corium. He described these elements in an exhaustive manner. They are small rodlike fibers, seven tenths of a micron in length, with obtuse ends and arranged in a parallel manner at the lower pole of the basal cells (fig. 1). Here and there they form meshes, but nowhere do they penetrate into the epithelium. Homma remarked that impregnation of the subepithelial lattice fibrils is difficult. ("Die optimale Grenzen der Imprägnierung sind hier sehr eng.") The processes of the epithelium are not seen by means of this impregnation.

3. Homma: Gitterfasern in normaler menschlicher Haut, Wien. klin. Wchnschr. **35**:149, 1922.

For this reason Homma did not deal with the relation between the basal layer and the subepithelial lattice fibrils. For their simultaneous demonstration, Welti [4] employed staining with magenta red and indigo-carmine (sodium indigotindisulphonas) after impregnation with silver. Tryb [5] employed for this purpose a ferric chloride-hematoxylin-picric acid combination. I tried with my method to stain intensively the epithelial spirals and the so-called fastening epithelial fibrils after the Bielschowsky-Maresch impregnation. Small pieces of human skin obtained from freshly made biopsies and immediately placed in Orth's

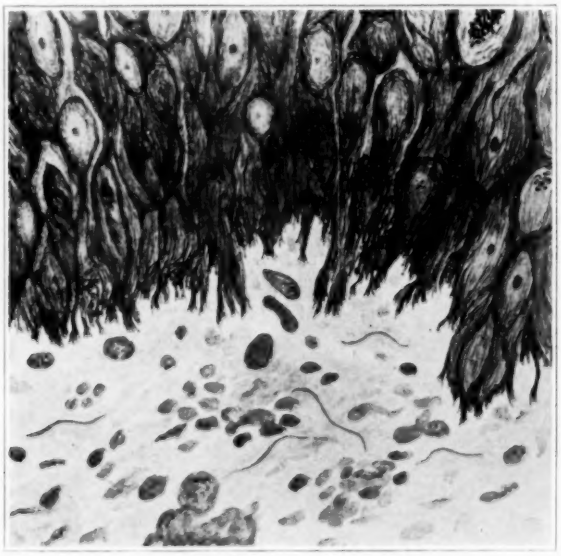

Fig. 2.—The inferior surface of the basal layer with their flabelliform processes. Acid fuchsin stain; mordanted in a 1 per cent solution of phosphomolybdic acid.

fixation fluid were used. After fixation, paraffin sections were made. Then the Bielschowsky-Maresch silver impregnation was performed, after which the sections were stained with acid fuchsin dye and mordanted in a 1 per cent solution of phosphomolybdic acid for from one to two hours. By this procedure the epithelial fibrils of the inferior surface of the basal layer with their flabelliform processes ("Haftfasern" and "Wurzelfasern," as they are called by German authors) are brought out clearly. These epithelial elements of the junction of the epidermis and the corium are light red and the silver-impregnated subepithelial fibrils

4. Welti: Ueber die morphologischen Beziehungen zwischen Epidermis und subepithelialem Stratum, Arch. f. Dermat. u. Syph. **146**:497, 1929.

5. Tryb: Ueber eine seltene Erkankung der Haut, Arch. f. Dermat. u. Syph. **143**:428, 1923.

are black (figs. 2 and 3). By this means a careful examination can easily be carried out. In most cases the epithelial fastening fibrils do not take such a straight course as that outlined by Welti.

After examining material by the combined impregnation method, Welti came to the conclusion that the subepithelial lattice fibrils do not have an intimate connection with the basal layer and its fastening fibrils.

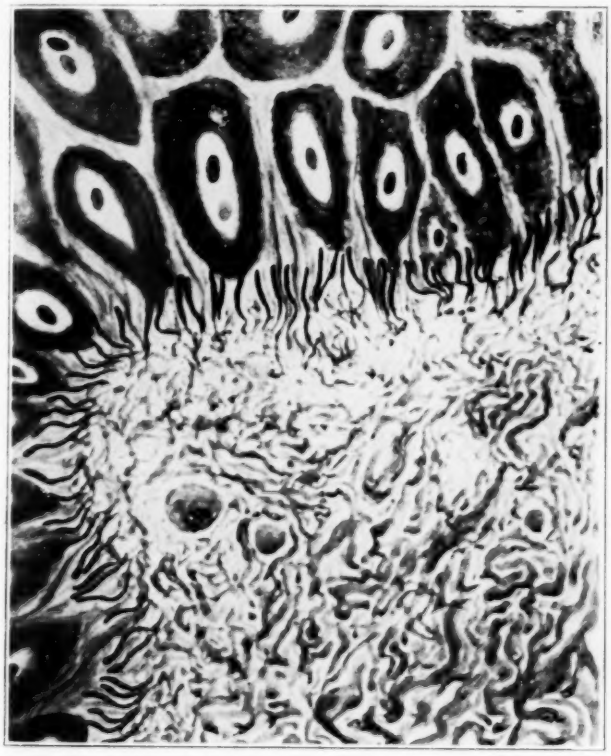

Fig. 3.—The epidermis-corium boundary of the skin of the forearm. Silver impregnation and acid fuchsin stain.

In the examination of my preparations I found that these elements in general show a uniform behavior in this respect. In areas where the papillae are not high, especially in the top of the papillae, the black lattice fibrils fit into the interspaces of the basal layer formed by the processes of the epithelial cells (fig. 3). In places one can see longer epithelial fibrils penetrating between the fibers of the connective tissue. The connection between the basal layer and the corium resembles generally that of two brushes fitted together along their bristle surfaces. A continuous and intimate connection exists between these elements as

already observed by Tryb and Kogoj.[6] These authors described them as "clinging to one another" (fig. 4).

Approximate cross-sections were made of the areas of the skin where the papillae are high, e.g., the skin of the sole and the palm. In some cases also the side of a papilla was visible. This picture was striking. The interspaces of the lattice work of the papilla, arranged in a parallel manner, were nearly filled by rather long elements stained a light red; they were therefore assumed to be the processes of the basal layer radiating from the side of the papilla into the spaces of the argyrophil lattice work; by this means, the firmness of the connection is strengthened. Particularly in sections cut in a more oblique plane, it was seen that even the subepithelial lattice fibrils do not take always a straight course. In obliquely cut sections, argyrophil fibrils could be observed in their entire length in the plane of the section. In some epithelial ledges that were cut diagonally, lattice fibrils coming from the subepithelial lattice work were seen penetrating between the epithelial cells (fig. 5) and embracing the epithelial cells together with their processes which are known to be part of the epithelial cytoplasm, for experiments

Fig. 4.—The connection between the processes of the basal cells and the subepithelial lattice fibrils in the skin of the sole.

6. Kogoj: Ueber die Art der Verbindung zwischen Epidermis und Kutis, Dermat. Ztschr. **39**:203, 1923.

have shown that they also contain pigment granules. From the evidence of these pictures it is undeniable that there is some means of firm joining between the two layers.

Fine ramified elastic fibrils are the third element that plays a rôle in the formation of the junction of epidermis and corium. They originate in the elastic tissue of the papillae. Their chief branches, as a rule, are arranged parallel with the junction of the epidermis and the corium just beneath the basal layer. From these fibrils delicate vertical ramified orceinophil fibrils pass to the basal layer. To investigate these, one must stain the paraffin sections with a well matured Tänzer orcein

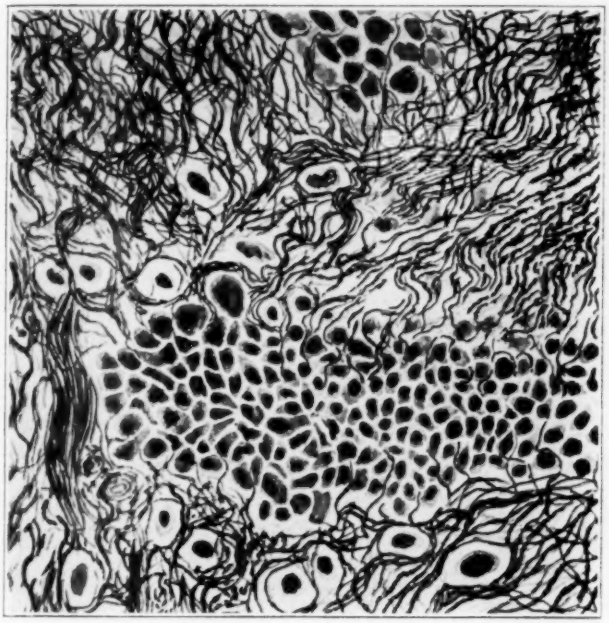

Fig. 5.—A diagonally cut epithelial ledge and the lattice fibrils of the papillar layer penetrating between the epithelial cells.

solution and place them in the aforementioned acid fuchsin-phosphomolybdic acid combination. The study of these elastic fibrils has been neglected by modern writers. Their stretched state, their ramifications directed toward the basal layer and their penetration into the processes of the epithelium point to the importance of their rôle in the connection between the epithelium and the corium.

CONCLUSION

In this paper, written from a purely histologic standpoint, I would insist that a complete and firm connection exists between epithelium and corium as manifested under physiologic and pathologic conditions.

TULAREMIA

REPORT OF AN UNUSUAL CASE *

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Up to 1924, only 15 cases of human tularemia had been described. Since that time more than 800 cases have been reported in the literature, and one cannot escape the conviction that the disease is widespread at present. Cases have been reported from every state in the Union, except the New England states, Delaware and Washington, as well as from Japan and Russia.

Under these conditions, cases varying from the typical are likely to occur from time to time. An unusual case of well proved human tularemia forms the basis for this report.

For a complete bibliography and an exposition on the various phases of tularemia, reference should be made to the excellent book by Simpson,[1] published in 1929.

REPORT OF CASE

A. K., a farmer, aged 67, whose home was in northern Michigan, presented himself at the clinic on June 3, 1930, complaining of an ulcer on the abdominal wall and tender swellings in the right groin, on the wall of the right side of the chest and in the right axilla. The past history, except for the facts that bear on the infection, was of little importance.

Examination revealed a somewhat senile male patient with an ulcer on the abdominal wall and the subcutaneous swellings already mentioned. The ulcer was on the right side of the abdominal wall; it was roughly oval and about the size of a quarter. The base was necrotic, and the discharge was moderately purulent. The border of the ulcer was distinctly elevated, only moderately firm and slightly tender; while it was red, it took the bluish tinge that is commonly seen with the infectious granulomas rather than with acute inflammatory processes.

The swellings in the right axilla and the right groin were the size of a walnut and obviously glandular. The surfaces of these swellings were reddened; on palpation, they were fluctuant and mildly tender. The swelling in the right pectoral region was the size of a cherry and neither red nor tender, although it later became fluctuant.

The proper diagnosis was not made at the original examination, but because of the many possible diagnoses, the axillary lymph node was excised for micros-

* Submitted for publication, Sept. 26, 1930.

* Studies and Contributions of the Department of Dermatology and Syphilology, University of Michigan Medical School, Service of Dr. Udo J. Wile.

1. Simpson, W. M.: Tularemia, New York, Paul B. Hoeber, Inc., 1929.

copic study, and a specimen of blood was sent to the laboratory for agglutination tests. The central laboratory immediately reported that the agglutination was characteristic of tularemia in a dilution of 1:320. The diagnosis from the department of pathology read: "Late acute or early subacute lymphadenitis characterized by multiple abscesses, caseation and epithelioid areas. It looks more like tularemia than anything else. We would like to know the result of agglutination tests."

With this suggestive information, the following story was obtained from the patient: On April 26, 1930, he attended a sale at which he bought nine of a group of fifteen rabbits. While he acknowledged that he was not familiar with

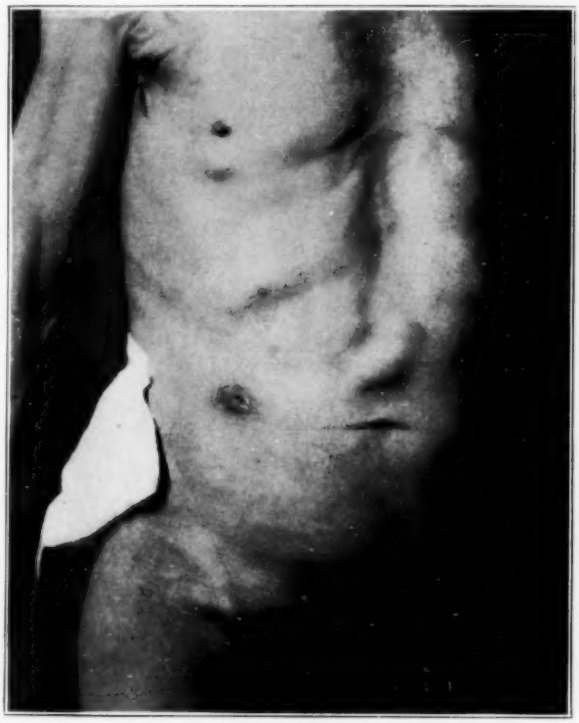

Fig. 1.—Patient having tularemia, showing the unusual location of the primary sore on the abdominal wall and the inguinal, pectoral and axillary adenitis.

the various breeds of rabbits, he was sure that they were not of the cottontail or of the snowshoe type; they were represented to him as chinchillas. On the following morning, one rabbit was found dead, and a neighbor, who had also bought rabbits at the same sale, came to the patient's home for the purpose of replacing one of his animals that had died during the night. During the next few weeks, seven of the nine rabbits died, and the final two were liberated because it was felt that they were dying from restraint and lack of proper food. Obviously, these rabbits had a serious infection, and the suggestion is that they had tularemia, although that cannot definitely be proved.

Early in May, or about a week or ten days following the acquisition of the rabbits, the patient was grading a road, and at that time he felt ill, and began

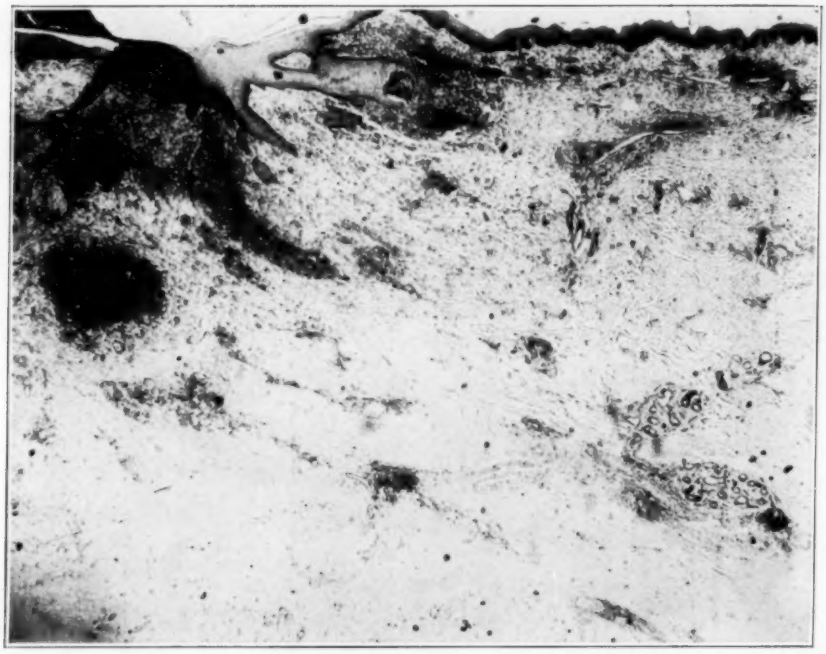

Fig. 2.—A biopsy specimen from the border of the primary sore, showing the wide extent and the perivascular and periglandular distribution of the infiltrate; low power magnification.

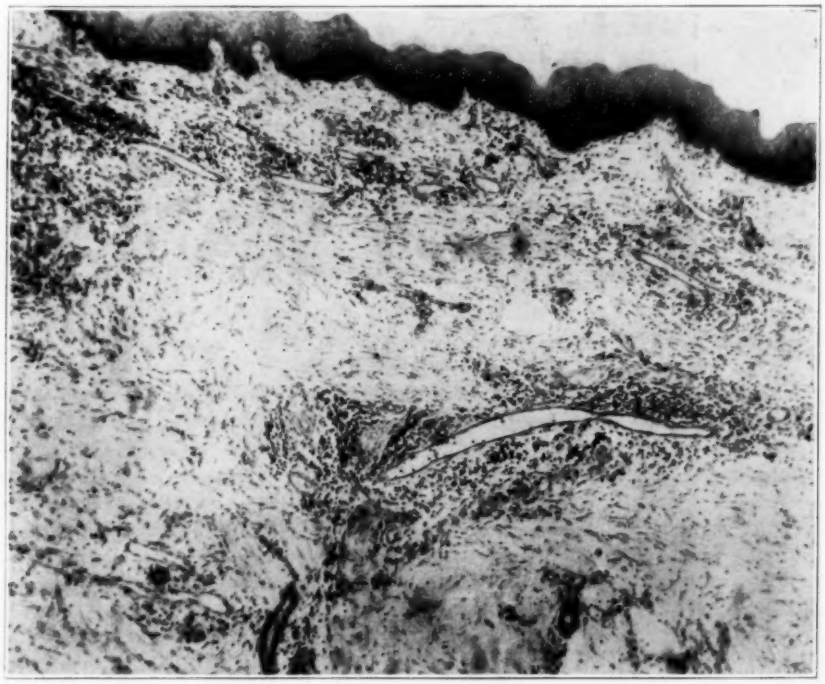

Fig. 3.—Distribution of the infiltrate; slightly higher power magnification than in fig. 2.

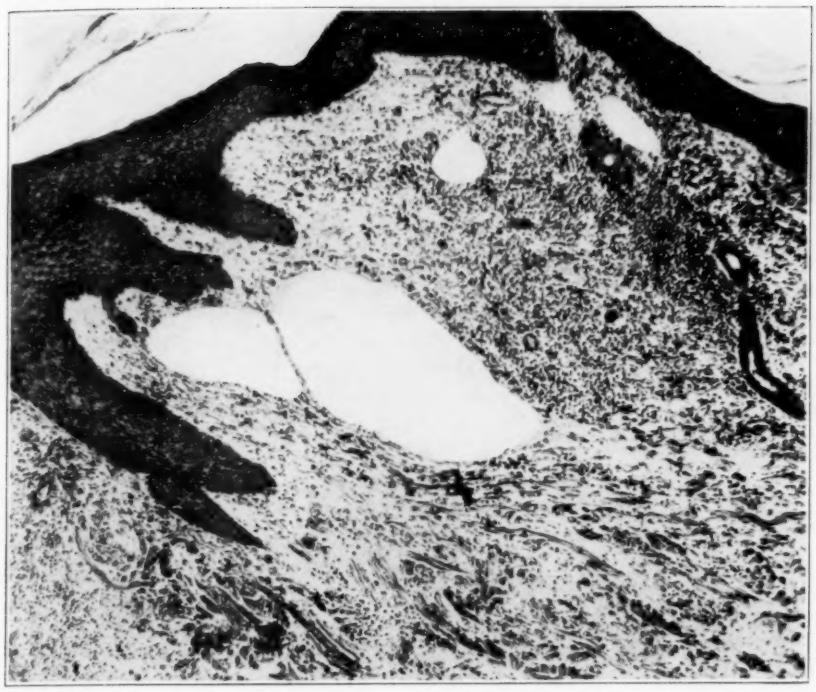

Fig. 4.—Massive infiltrate of cells near the border of the ulcer, showing the formation of giant cells.

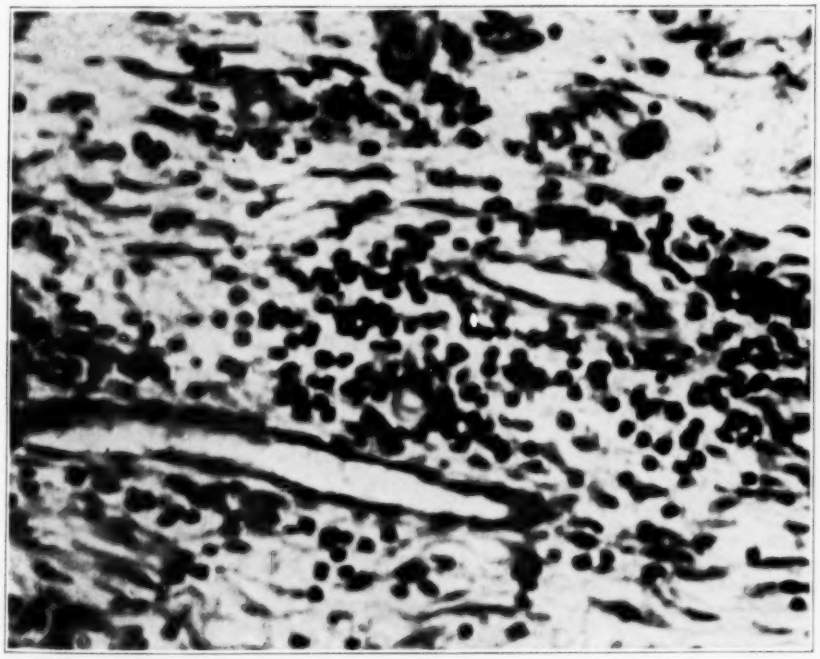

Fig. 5.—The mononuclear type of cell in the infiltrate—largely plasma cells; high power magnification.

to lose weight. His muscles and joints ached and were sore, and he thought that the heavy work had been too much for him. About the same time, there developed a lesion on the abdominal wall, which he thought was a boil, and the axillary and inguinal swellings appeared. In point of time, he was unable to place one of these lesions ahead of the other, and he thought that they all appeared about the same time. Consequently, it was thought that the patient was in the fourth or fifth week of his illness when I saw him on June 3.

Laboratory Observations.—Pus from the inguinal lymph node was inoculated into the abdominal wall of two guinea-pigs; these animals died on the fifth day. Other guinea-pigs were inoculated with material from the spleens of these animals, and splenic material was cultivated on blood-cystine agar. The culture produced *B. tularensis;* this organism was inoculated into the abdominal wall of two more guinea-pigs. These animals died on the fifth day; the spleen and the liver shown in figures 6 and 7 are from these animals. Macroscopically, these are the typical

Fig. 6.—Spleen of a guinea-pig, showing typical lesions of tularemia. This animal died five days after inoculation.

lesions of tularemia, and microscopically, they show the typical focal necroses that have previously been thoroughly described.[1] In all, eight guinea-pigs were inoculated with pus from the inguinal lymph node of the patient, from the splenic material and from the culture obtained from the splenic material. All of the animals died between the fourth and the sixth day; all showed characteristic changes of tularemia in the spleen and the liver.

Pathology of the Primary Lesion.—Netherton [2] was probably the first to recognize the pathologic condition of the primary lesion of tularemia in man as that of an infectious granuloma. In the case here reported the specimen for biopsy was taken from the border of the primary lesion about five weeks after its appearance, and the results of the biopsy bear out his observations. Aside from mild acanthosis, the chief changes were in the corium, consisting of a perivascular

2. Netherton, E. W.: Tularemia with Reference to Its Cutaneous Manifestations, Arch. Dermat. & Syph. **16**:170 (Aug.) 1927.

and periglandular infiltrate of mononuclear cells, largely plasma cells. The distribution is shown in figures 2 and 3. Figure 4 shows a much more dense infiltrate in the upper portion of the corium; in it there is a distinct formation of giant cells. Figure 5 shows the mononuclear character of the infiltrate.

While some of the vessels showed a mild endarteritis, this feature was not as prominent as that described by some observers.

Unusual Features of the Case.—The features making this case unusual were: (1) the location of the primary lesion, (2) the season in which the infection was acquired and (3) the type of rabbits concerned.

In order to compare the unusual features, it will be necessary to review briefly the usual characteristics of tularemia. While many ani-

Fig. 7.—Liver of a guinea-pig, showing typical lesions of tularemia. The liver in this figure and the spleen shown in figure 6 are from the same animal.

mals have been shown to be potential sources of infection, the great actual sources are wild rabbits, wood-ticks and the so-called deer flies. Since actual injury during the handling of wild rabbits usually determines the location of the primary lesion, the latter is ordinarily found on the hands, and the adenitis is commonly epitrochlear and axillary. The next most common location for the primary lesion is the conjunctiva; a few unusual locations about the head and the legs have been described by Simpson,[1] Miller and Taussig [3] and others.

3. Miller, H. E., and Taussig, L. R.: Tularemia, Arch. Dermat. & Syph. **19**:378 (March) 1929.

These unusual locations are commonly due to bites of flies or woodticks rather than to injury during the handling and dressing of wild rabbits.

It has been shown that there is a marked difference in seasonal incidence west and east of the Mississippi River. In the West, where wild rabbits are not ordinarily protected by law, and where apparently a large proportion of the cases have been due to bites by flies and woodticks, cases are reported during practically every month. East of the Mississippi, however, wild rabbits are protected, except during the fall and early winter, and apparently most of the cases have been due to actual injury while the animals were being handled. Simpson [1] stated that practically all cases east of the Mississippi, except a few in the southern states, have occurred in November, December and January, which coincides with the hunting season.

Up to the present, no case of tularemia that was acquired from tame rabbits has been reported, although there have been many cases in laboratory workers apparently acquired from laboratory animals purposely inoculated.

The location of the primary lesion in this case is distinctly unusual and difficult to explain. This patient absolutely denied any contact with wild rabbits during the five years previous to his illness, and infection from deer flies can be ruled out by reason of the usual temperatures in northern Michigan during April and early May. Woodticks cannot be ruled out as a possible source of the infection. Knowing that this patient came into contact with seriously infected rabbits shortly before his illness began, one cannot escape the conviction that the infection came either directly or indirectly from them.

If one grants the cause and effect, it is still difficult to account for the location of the primary lesion. The patient said that he helped carry the box containing the rabbits, and that this came in contact with his clothing, but he did not recall an injury that would account for the lesion on the abdominal wall.

The next unusual point in this case is the seasonal variation, which would seem to rule out infection from wild rabbits as well as from deer flies, and which lends additional evidence to the suggestion that the disease was acquired from tame rabbits.

At this time, there is no possible way of determining the exact variety of rabbits concerned in this case. They were represented to the patient as chinchillas, but he admitted that he was not sure of the breed. It is possible that the original rabbits were of that breed, but one cannot be sure that recently caught wild rabbits were not added to the pen for the sale. As far as can be determined, all of the rabbits concerned in the sale are either dead or liberated, so that the question as to whether or not this infection occurred from tame rabbits must be

left unsettled. The facts in the case, however, have been given to Dr. Don M. Griswold of the Michigan Department of Health, and he is attempting to get added information as to the source and the type of rabbits concerned.

Course and Treatment.—The patient remained at the hospital from June 3 to July 17. During this time he showed a mild septic type of fever, moderate anemia and practically no leukocytosis. The temperature curve became practically flat during the week before his discharge.

Treatment consisted of rest in bed, excision of the axillary lymph node, incision and drainage of the other two enlarged lymph nodes and local wet dressings. No other treatment was used except a dietary in an attempt to build up the general condition. It might be worth while to note that the incision that was made in removing the axillary node healed by primary intention and much more rapidly than the pectoral and inguinal regions, where the incision was followed by drainage. The primary lesion healed without difficulty in about two weeks with simple boric wet dressings.

COMMENT

At this time it seems appropriate to point out that a positive agglutination test does not necessarily mean that the patient has active tularemia. Several authors (Simpson [1]) have shown that the agglutination test remains positive for tularemia for several years, and, perhaps, permanently, after all evidence of the active disease has disappeared. Typhoid fever and tuberculosis can be closely simulated by this disease, and the persistence of a positive agglutination test might easily lead to an error. While a positive agglutination test, together with a suggestive train of signs and symptoms, is presumptive evidence that the patient has tularemia, to prove this, isolation of the organism and reproduction of the disease are required.

SUMMARY

A case of tularemia is presented that is unusual in the site of the primary lesion, in the season in which the infection was acquired and, I believe, also in the type of animal concerned in the transmission. While absolute proof that this infection is from domesticated rabbits is lacking, I believe this is true, and I think that I have fair evidence for the belief. Even if I am wrong on this point, the unusual location of the primary lesion in the case would justify this report.

Prof. Udo J. Wile permitted me to present this work. Miss Lucy D. Henry, of the Bacteriology Department, and Mr. Harry Minckley, of the Roentgenology Department, assisted with the bacteriologic experiments and the photography, respectively.

UREMIC DERMATITIS *

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CHICAGO

It was thought for a long time that diseases of the skin predisposed to nephritis. This was explained by a suppression of the function of the skin that resulted in nitrogenous retention and albuminuria. Partial varnishing of the skin of man, however, failed to produce albuminuria (d'Edenhurzen and Lomikowsky [1] and Senator [2]).

Thibierge [3] (1885), on the strength of these and other experimental studies, in addition to his own clinical material, reasoned that the same noxa that caused nephritis might also cause the manifestations of the skin. Jadassohn [4] observed that, although albuminuria accompanied certain lesions of the skin, it did not necessarily denote nephritis, for in many instances the albuminuria disappeared with the dermatitis.

The explanation then offered, and the one now accepted, for the lesions of the skin occurring with true nephritis was that the nephritis was primary and the dermatitis secondary, the latter resulting from a noxa produced by the nephritis (Merk,[5] Block,[6] Chiari,[7] Walthard,[8] Gruber [9] and Rössle [10]).

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* Submitted for publication, Aug. 23, 1930.

* From the Department of Pathology, Cook County Hospital.

1. d'Edenhurzen and Lomikowsky, quoted by Thibierge, G.: Ann. de dermat. et syph. **6**:511, 1885.

2. Senator, H.: Wie wirkt Firnissen auf die Haut des Menschen? Virchows Arch. f. path. Anat. **70**:182, 1877.

3. Thibierge, G.: Dermatoses et Albuminurie, Ann. de dermat. et syph. **6**:511, 1885.

4. Jadassohn, J.: Hautkrankheiten bei Stoffwechsel-Anomalien, Internationaler Dermatologen-Kongress, Berlin, 1904.

5. Merk, L.: Dermatoses Albuminuricae, Arch. f. Dermat. u. Syph. **43**:469, 1898.

6. Block, H.: Beziehungen zwischen Hautkrankheiten und Stoffwechsel, Ergebn. d. inn. Med. u. Kinderh. **2**:521, 1908.

7. Chiari, H.: Ueber einen Fall von urämischer Dermatitis, Prag. med. Wchnschr. **36**:30, 1905.

8. Walthard, B.: Zur Lehre der urämischen Hautveränderungen, Frankfurt. Ztschr. f. Path. **32**:8, 1925.

9. Gruber, G. B.: Ueber die Pathologie der urämischen Hauterkrankungen, Deutsches Arch. f. klin. Med. **121**:242, 1916-1917.

10. Rössle, R.: Urämische Dermatitis, Virchows Arch. f. path. Anat. **271**:304, 1929.

In nephritis the following lesions of the skin have been described:

I. Nephritis without uremia

(*a*) Prurigo, (*b*) urticaria, (*c*) eczema (Thursfield[11] and Chiari[7]).

II. Nephritis with uremia.

(*a*) Prurigo with universal erythema (Thibierge,[3] Walthard[8] and Rössle[10]).

(*b*) Maculopapular or vesicular eruption (Huet,[12] Bruzelius,[13] Chiari,[3] Gans,[14] Gruber[9] and Rössle[10]).

(*c*) Purpura or other hemorrhagic changes in the skin (Thursfield,[11] Fox,[15] Marchand[16] and Kaulen[17]).

(*d*) Necrotic lesions of the skin (Chiari,[7] Walthard,[8] Dalche and Claude[18]).

These manifestations of the skin have been described in association with nephritis and they are considered by some to be specific (Huet,[12] Bruzelius,[13] Block[6] and Pfaundler[19]). It is more generally accepted that except for pruritus and erythema, there are no specific lesions of the skin in nephritis.

The explanation offered is that some injurious agent resulting from the dysfunction of the kidney causes necrosis of the capillary endothelium and hyaline thrombi. These changes lead to hemorrhages in the cutis and to necrosis of the epidermis. Polymorphonuclear leukocytes and lymphocytes infiltrate the necrotic and hemorrhagic areas as a result of the irritation (Chiari[7] and Rössle[10]), or as a result of secondary infection (Gruber[9] and Walthard[8]).

The importance of the subject and the relative infrequency of systematic histologic studies of the skin in nephritis have been an impetus for this study.

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11. Thursfield, H.: Hautkrankheiten bei Brightscher Krankheit, Frankfurt. Ztschr. f. Path. **32**:12, 1925.

12. Huet, J.: Erythema papulatum uraemicum, Nederl. tijdschr. v. geneesk., 1870 and 1872; abstr., Ann. de dermat. et syph. **6**:511, 1885.

13. Bruzelius, A.: On Erythema Uraemicum, Ann. de dermat. et syph. **6**:511, 1885.

14. Gans, O.: Hauterkrankungen bei Urämie, Berlin, Julius Springer, 1925, vol. 1, p. 155.

15. Fox, C.: Hemorrhagic Erythema in Bright's Disease, Lancet, June, 1899; abstr., Wchnschr. f. prakt. dermat. **30**:181, 1900.

16. Marchand, F., in Marchand and Krehl: Handbuch der allgemeine Pathologie, Leipzig, 1915, vol. 2, p. 297.

17. Kaulen, G.: Ueber Hautblutungen bei Urämie, Monatschr. f. Kinderh. **22**:599, 1922.

18. Dalche, P., and Claude, H.: Ulcerations hemorragiques de la peau et des muqueuses dans l'urémie, Bull. et mém. Soc. méd. d. hôp. de Paris **20**:75, 1903.

19. Pfaundler, M., and von Seht, L.: Zur Systematik der Blutungsübel im Kindesalter, Ztschr. f. Kinderh. **19**:225, 1919.

MATERIAL

The dermatologic observations here recorded are based on eighty-nine cases, in which the renal pathologic process was the primary cause of death. Of these, there were thirty cases of primary contracted kidneys, twenty-seven of chronic glomerulonephritis, fourteen of subacute glomerulonephritis, eight of acute glomerulonephritis, nine of pyelonephritis and one of amyloid contracted kidneys. There were fifty-six cases associated with uremia. Histologic examinations were performed in forty instances.

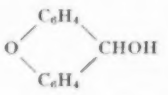
METHODS

Sections of skin were taken from the chest and the abdomen in each of the forty cases and placed in two fixing solutions: a diluted solution of formaldehyde, U. S. P. (1:10) and a 6 per cent solution of xanthydrol in glacial acetic acid.

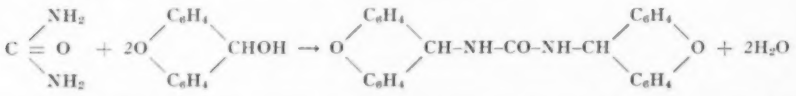
Frozen and paraffin sections were made of the formaldehyde-fixed material. The stains used in all instances were hemalum and eosin and, when necessary, oxydase, sudan III, elastica, Giemsa, Unna-Pappenheim and Bielschowsky.

The technic of using xanthydrol is described in detail, because it had not yet been utilized in this country.

Xanthydrol is a white powder which, microscopically, is composed of prismlike crystals. Its ability to unite with urea in the tissues has been emphasized by Oestreicher.[20] Its formula is (Oestreicher):



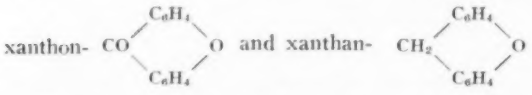
and, on combining with urea it forms dixanthylurea:



It is a light, yellowish-green, needle-like, crystalline substance which radiates from a central nucleus.

The dixanthylurea crystals are doubly refractive; they are not soluble in water, alcohol, ether or xylene, but are soluble in phenolxylene.

To facilitate the reaction, the xanthydrol is dissolved in glacial acetic acid. The acetic acid acts as an extractor of water. The mixture is allowed to stand for from one to two hours before using in order to dissolve the xanthydrol completely. If kept for over seventeen hours, the solution decomposes into



Thin pieces of skin, not more than 2 or 3 mm. in thickness, are placed in the 6 per cent solution of xanthydrol and acetic acid and allowed to stand for from

20. Oestreicher, A.: Ueber den Nachweis des Harnstoffes in den Geweben. mittelst Xanthydrol, Virchows Arch. f. path. Anat. **257**:614, 1925.

ten to fifteen hours. The tissues are then placed in absolute alcohol for forty-eight hours, xylene for one hour, xylene paraffin for one hour and clean paraffin (52 C.) for four hours at a uniform temperature of 55 C. The tissues are embedded in clean paraffin (56 C.).

The sections are cut from 5 to 6 microns thick and may or may not be stained.

The method of staining used, which was found to be satisfactory, is as follows: Stain with hemalum for five minutes, and with eosin (0.1 per cent) for thirty seconds; decolorize with acid alcohol for one second; clear with absolute alcohol and xylene, and mount in balsam.

By this procedure, the nuclei and cytoplasm are pale but distinct, while the crystals are yellowish green and prominent.

RESULTS

Macroscopic Observations.—Grossly, the skin did not present any characteristic indications except for a granular white precipitate that was most common about the nose, the neck and the shoulders, but was also found on the chest, the trunk and the extremities. It resembled table salt and was easily removable. This phenomenon occurred in thirty-three of the fifty-six cases of uremia.

The skin itself was coarse, dry and scaly and, occasionally, petechial hemorrhages were noted. The latter occurred in thirteen of the eighty-nine cases of nephritis, twelve being in cases of uremia. The most common site was on the trunk and the conjunctiva.

As a matter of comparison, there were sixty-eight cases in which the viscera had petechial hemorrhages. All of the cases of uremia (fifty-six) were thus affected. The most common site was the gastro-intestinal tract.

Microscopic Observations.—Normal Considerations: A series of normal studies was carried out on patients of varying ages to determine the number of layers of cells that composed the epidermis (pieces of skin were taken from the chest and the abdomen). On an average, in persons between the ages of 12 and 45 years, the papillae were composed of eight layers of cells and the interpapillary areas, three layers of cells. In persons over 45 years, the number of layers gradually diminished, and up to 70 years they averaged from about two to six. In the latter, the papillae were moderately flattened, and pyknotic nuclei were noted in the rete mucosum.

The corneum in these cases was thick and varied from one to three times the thickness of the rete malpighii. This was true of all of the cases studied, as was expected, because the majority of the patients at the County Hospital are laborers and their clothes are usually made of rather coarse material. Also, 50 per cent of the cases studied were in colored persons.

Cases Studied: The average age for the forty patients in whom the skin was examined microscopically was 40 years. Because of a

definite relationship between the clinical and the anatomic time element of the renal lesion and the microscopic observations on the skin, the pathologic histology of the skin will be described according to the duration of the disease.

Cases of a duration of from one week to one month include six of acute glomerulonephritis, six of subacute glomerulonephritis and four of malignant nephrosclerosis.

As already stated, the corneum was thickened, and stained a homogeneous pink with eosin. It was composed of longitudinal layers and the outermost layer stained light orange with sudan III.

In the cases of short duration, the number of layers of cells of the rete mucosum was about normal and varied from two to six layers to three to nine layers. The papillae were prominent and showed only a slight tendency to flattening. The cells proper were swollen and their nuclei were palely stained. Some of the nuclei were shrunken, being deep blue and assuming crescent shape. The latter were surrounded by crescent-shaped vacuoles. In some areas, the nuclei had entirely disappeared and had left a pale pink area. This was in turn surrounded by pyknotic nuclei. The intercellular bridges were indistinct.

The basal layer showed similar changes, but, in addition, some of these cells had become detached and were found in the cutis. The identity of the cells in the cutis with those of the epidermis was borne out by special fixing of the tissues (Bouin's and Zenker's solutions) and by staining with Giemsa's and Unna-Pappenheim's methods.

The nuclei of the detached cells were similar to those of the columnar layer. They were round or oval with distinct nuclear membranes. The chromatin was scanty and was finely and coarsely granular. The larger granules appeared to be connected by a fine reticulum. Each cell contained an oxyphilic nucleolus which was situated somewhat off from the center. At times, basal cells with pyknotic nuclei were found in the papillary layer of the cutis.

The capillaries of the cutis were dilated, and their endothelial cells were swollen. In some instances, when red blood cells were found loose in the stroma, capillaries in that vicinity were found in which there was a break in the continuity of the endothelium. The cells adjacent to this break were shrunken, and their nuclei were pyknotic.

The lymph channels were also dilated, and the endothelial cells lining them were swollen. There was a perivascular infiltration with round cells which was moderate in amount and not more than was found in the control studies. The oxydase reaction of the perivascular infiltration was negative.

The sudoriferous and sebaceous glands showed little change. The nerves were free from changes or perineural infiltration with round cells.

The stroma of the reticular layer stained light pink, and histiocytes with elongated, oval nuclei and mast cells were scattered throughout. These were most abundant in the papillary layer, and sometimes they invaded the epidermis.

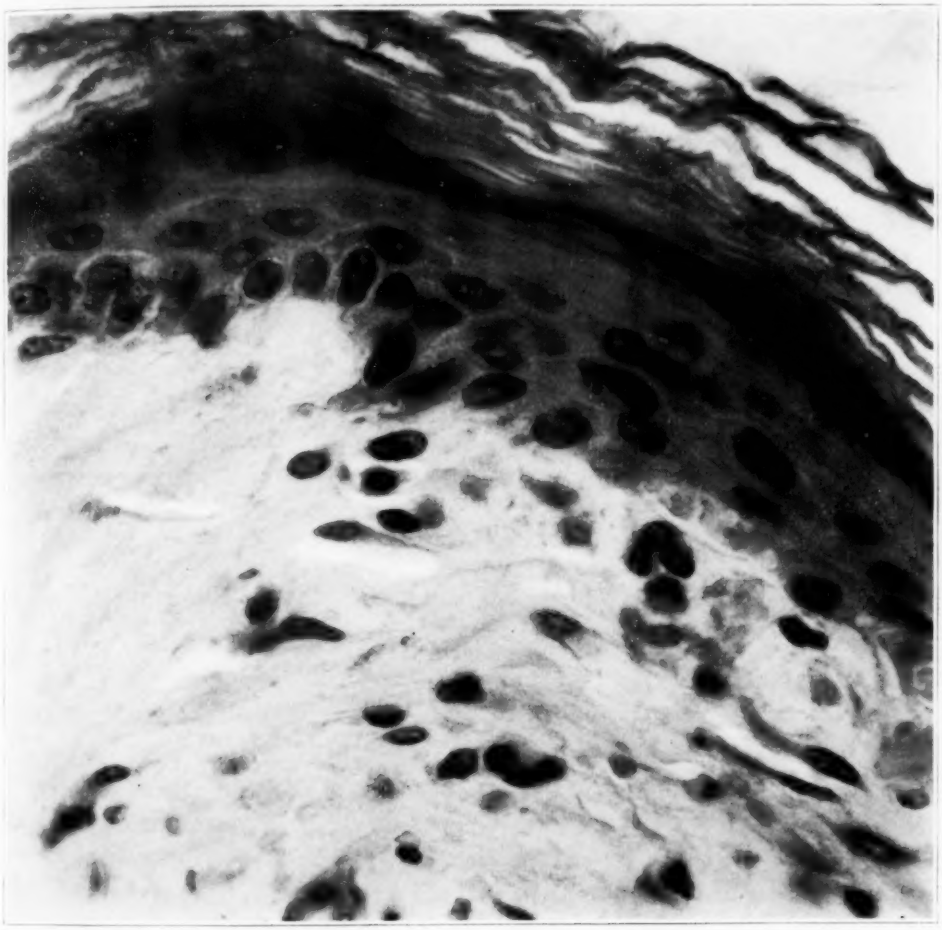


Fig. 1.—Cells of the columnar layer of the epidermis free in the papillary layer of the cutis, from a case in a woman, aged 35. Note the flattening of the epidermis and the thickness of the corneum. Oil immersion; × 900.

The cases of a duration of from one to four months include four of chronic glomerulonephritis, five of malignant nephrosclerosis and two of pyelonephritis.

The layers of cells in the rete mucosum varied from two to five to two to six. The papillae showed a moderate flattening. The cells

were round or oval and their nuclei stained a pale blue. There were a greater number of pyknotic nuclei and vacuolization of the cytoplasm. Small areas staining a homogeneous pink and surrounded by pyknotic nuclei were more numerous than in the cases of a duration of from one week to one month.

The cells of the basal layer presented more pyknotic nuclei; some of these cells, as well as the apparently normal ones, were found free in the papillary layer of the cutis.

The changes in the cutis were similar to those in the foregoing group, except that the cells of the sudoriferous and sebaceous glands showed pyknotic nuclei.

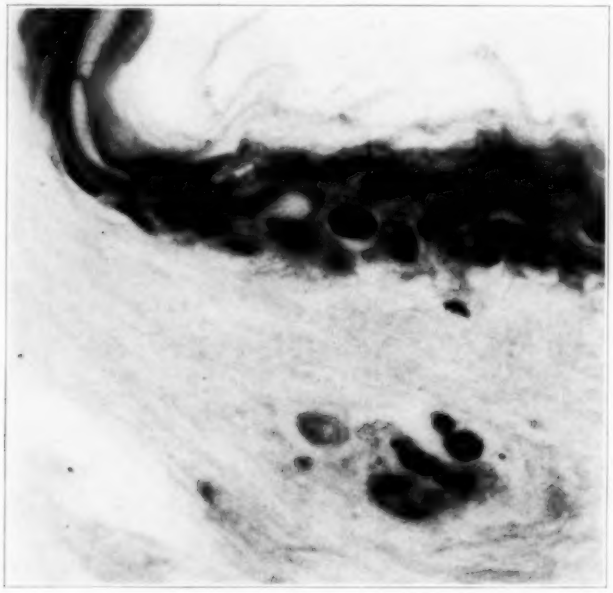


Fig. 2.—Marked flattening of the epidermis, showing pyknosis of the nuclei and vacuolization of the cytoplasm, from a case in a man, aged 30. Oil immersion; × 900.

The cases of a duration of from five to twelve months include one of subacute glomerulonephritis, one of chronic glomerulonephritis, four of malignant nephrosclerosis and four of benign arteriolosclerosis.

The average number of layers of cells in the rete mucosum was from two to four. The flattening of the papillae was more marked. The cellular changes were similar to those in the cases of less duration but they were more advanced.

The changes in the cutis were similar to those in the cases of less duration.

The cases of a duration of fifteen months and over include two of chronic glomerulonephritis, two of malignant arteriolosclerosis and one of benign arteriolosclerosis.

The number of layers of cells in the rete mucosum varied from none to three to one to three. The papillae were markedly flattened; in many instances they were absent. Where the rete mucosum was thin or absent, the skin was still intact as the thick corneum was not broken.

The cells, for the greater part, showed pyknotic nuclei with vacuolization of the cytoplasm. The pyknotic nuclei of the basal layer were found in the papillary layer of the cutis.

The number of capillaries and lymph spaces in the cutis were noticeably reduced. The cells of the endothelial lining were shrunken and the nuclei were pyknotic.

The sudoriferous and sebaceous glands were reduced in number, and in many instances, they were not seen in the section. An occasional remaining gland showed marked atrophy. The nuclei of the epithelial lining were either pyknotic or absent.

The elastic fibers of the reticular zone, in most instances, were uniformly distributed as distinct fibers. In some instances, there were clumps of elastic fibers matted together by a homogeneous basophilic substance. These areas were most common in the upper portion of the reticular zone.

STUDIES WITH XANTHYDROL

The skin normally does not excrete an appreciable amount of urea, as was shown by the dixanthylurea reaction. Normally, a complete absence of crystals to two or three crystals per low power field were noted. As a rule, the amount of urea in the skin was directly proportional to the amount in the blood.

In uremia, the crystals were found in the subcutaneous fat, the cutis, the lymph, the blood vessels, the sebaceous and sudoriferous glands and in the epidermis, including the cells proper and the intercellular spaces. The papillary layer of the cutis and the rete mucosum contained the largest amount of crystals. At times these were so numerous as to obscure the histologic picture.

It was of interest to note that the presence of dixanthylurea in the cell was, as a rule, not associated with a demonstrable alteration of the nucleus or cytoplasm, so that it appeared that urea by its direct action, even in the high concentrations as existed, was nontoxic. (The urea of the blood varied from 80 to 190 mg. per hundred cubic centimeters of blood.)

In one case of malignant nephrosclerosis with extensive hemorrhages in the cutis, the number of crystals in the skin was within normal limits, yet there was definite necrosis of the capillary endothelium. This again emphasized the nontoxicity of urea and suggested the presence of a toxic precedent.

Studies with xanthydrol were also carried out on the colons in which pseudomembranous colitis was present. It was found that dixanthylurea crystals were in greater abundance here than in the skin; the entire wall of the colon was heavily impregnated with crystals, but they were most marked in the mucosa.

The submucosa was edematous, and the blood and the lymph vessels were dilated and filled with crystals. In one case in which the skin was atrophic and contained only a few crystals, the colon contained the largest amount in the series studied. This suggested that as the skin became atrophic with the disappearance of its glands, the excretion through the skin was diminished, being diverted through the large bowel.[21]

PATHOGENESIS

Urea passes through the membranes of the cells without injuring the cells (Gryns[22]), yet in high concentrations it is fatal to dogs (0.6 Gm. per hundred cubic centimeters of blood, Marshall and Davis[23]) and produces an asthenic type of uremia when fed to normal men in large quantities (Hewlett, Gilbert and Wickett[24]). However, a high content of urea nitrogen in the blood is found in cases of intestinal obstruction without clinical or anatomic signs of uremia (Tileston and Comfort[25]), and also typical cases of uremia have been described in which the urea nitrogen was low (28 mg. per hundred cubic centimeters of blood, Strauss[26]). It is believed, then, that there are antecedents of urea, intermediate between urea and ammonium carbonate (the x sub-

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21. Further studies in regard to the pathogenesis of pseudomembranous colitis are being carried out.

22. Gryns, G.: Osmotische Druck und Ionenlehre, Arch. f. d. ges. Physiol. **63**:86, 1896.

23. Marshall, E. K., and Davis, D. M.: Urea: Its Distribution in and Elimination from the Body, J. Biol. Chem. **18**:53, 1914.

24. Hewlett, A. W.; Gilbert, Q. O., and Wickett, A. D.: The Toxic Effects of Urea on Normal Men, Arch. Int. Med. **18**:636 (Nov.) 1916.

25. Tileston and Comfort: High Non-Protein Nitrogen in Acute Intestinal Obstruction, in Wells, H. G.: Chemical Pathology, Philadelphia, W. B. Saunders Company, 1925, p. 611.

26. Strauss, H.: Ueber Urämie, Berl. klin. Wchnschr. **52**:368, 1915.

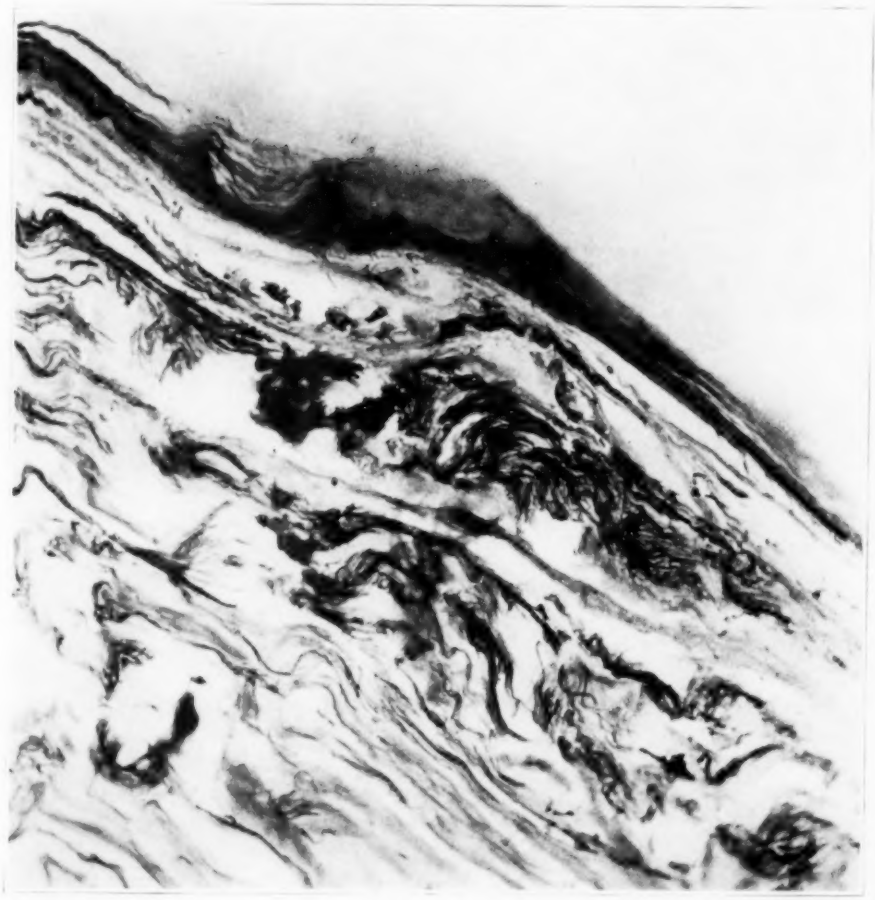

Fig. 3.—Clumping of the elastic tissue in the reticular zone of the cutis, from a case in a woman, aged 49. Elastica stain; × 100.

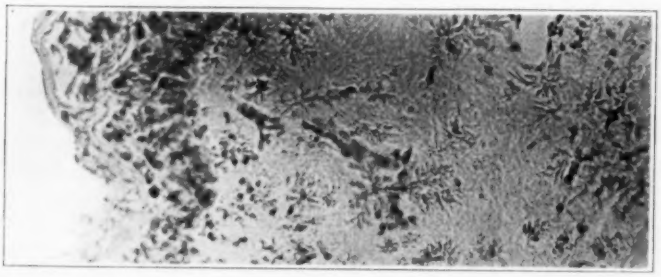

Fig. 4.—Dixanthylurea crystals in the epidermis and the cutis; × 250.

stance of Kendall;[27] ammonium carbonate, Marchand;[16] ammonium carbamate, Wells[28]) which are responsible for the uremic symptoms.

This substance may be the causative factor in the production of endothelial necrosis of the vessels of the skin, as the amount of urea in the skin in these cases was small. It may also account for the higher incidence of hemorrhages in the viscera, as the latter is the more natural outlet for nitrogenous substances.

The skin normally does not excrete urea but in uremia is called on to do so. The constant saturation and concentration did not act as a direct toxic irritant but its presence apparently displaced the normal afferent nutrient supply as well as the efferent catabolic return. This persistent state led to atrophy of the epidermis as well as of the cutis. The process was not a result of a generalized cachexia as the majority of the patients were well nourished.

The earliest changes were found in the epidermis. The cells of the rete mucosum were first swollen and their nuclei were pale. The nuclei then became pyknotic and the cytoplasm vacuolated. In places, the cells disappeared entirely and left a homogeneous oxyphilic area surrounded by cells with pyknotic nuclei.

The nuclei of the cells of the basal layer also became pyknotic and at times were found displaced in the papillary layer of the cutis. This might be explained by an initial loosening and displacement of the columnar layer, as a result of the oversaturation with urea, which was followed by atrophy and recession of the rete mucosum.

The changes in the cutis were simultaneous with those of the epidermis. At first, the capillaries and lymph channels dilated and their endothelial cells became swollen. The sessile histiocytes proliferated and were found to be most numerous about the blood vessels and in the papillary layer of the cutis. There was also a perivascular infiltration of round cells, but it was not beyond the normal limits. Mast cells were found in the cutis and occasionally in the epidermis.

As the disease progressed, the blood vessels collapsed and their endothelial cells shrank. There appeared to be a decrease in the number of capillaries.

The fate of the sudoriferous and sebaceous glands was similar to that of the blood vessels.

The elastic tissue of the cutis, as a rule, was unchanged but at times there appeared to be a clumping together of these fibers by a homogeneous basophilic substance.

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27. Kendall, E. C.: Experimental Hyperthyroidism, J. A. M. A. **69**:612 (Aug. 25) 1917.

28. Wells, H. G.: Chemical Pathology, Philadelphia, W. B. Saunders Company, 1925, p. 602.

COMMENT

The lesions of the skin in uremia as reported in this article, compared to those of German and Swiss authors, show a marked discrepancy and emphasize the importance of geographic pathology.

Although no explanation is offered for the wide variation in results, the following is suggested to explain the absence of dermatitis in the cases reported.

In every case the corneum was from one to three times as thick as the epidermis. In places where the epidermis was reduced to one layer of cells or to no cells, the corneum was still intact so that there was not a break in the continuity of the skin. This protective covering prevented the invasion of the epidermis by bacteria.

From a hygienic standpoint, the methods used in caring for the skin at the Cook County Hospital may have acted as prophylactic treatment. The patients received two sponge baths and two alcoholic rubs daily. After each procedure, talcum was applied freely.

The patients wore soft cotton shirts that were nonirritating to the skin, which were changed daily.

The thorough cleansing and disinfecting of the skin and its contact with soft, nonirritating clothing may also be an important factor in explaining the absence of dermatitis.

CONCLUSIONS

The characteristic macroscopic observation of the skin in uremia, as determined by this study, was a uremic frost.

The characteristic microscopic observations were essentially atrophy of the skin which was in direct proportion to the duration of the nephritis; it was not associated with a generalized cachexia.

The earliest changes which were found in the epidermis, consisted of a swelling of the cells, followed by pyknosis of the nuclei and vacuolization of the cytoplasm. The basal layer of cells undergoes similar changes and may be found free in the papillary layer of the cutis. The number of layers of cells of the epidermis decreases and may, in places, be entirely absent.

The cutis, together with the atrophic changes in the epidermis, shows collapse and disappearance of the blood and lymph vessels and of the sebaceous and sudoriferous glands.

The amount of urea in the skin as determined by the xanthydrol reaction is, as a rule, directly proportional to the amount of urea in the blood.

KERATOMA SENILIS AND VERRUCA SENILIS

A CLINICAL AND HISTOPATHOLOGIC STUDY *

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This study of keratoma senilis (senile keratosis) and verruca senilis (seborrheic keratosis) was undertaken because a definite, clearcut picture of the lesions could not be obtained from a review of the literature on the subject. I have attempted to show that the existing confusion with regard to these common lesions need not exist, that it is important to distinguish one lesion from the other, and that the lesions differ with respect to etiology, clinical and pathologic characteristics and prognosis.

CLINICAL CHARACTERISTICS

Keratoma senilis, when fully developed, presents a typical appearance. The lesions appear as sharply circumscribed, flat, elevated or verrucous, brownish, keratotic, scaling patches. They are usually situated on the face, hands and forearms, although they occur elsewhere on the body. Men are affected more often than women, as a rule after middle age and often in association with the changes of senile atrophy. The lesions begin as small, sharply circumscribed, yellow or brown spots, and may remain as such for many years. After varying periods, usually a number of years, many lesions become elevated and covered with firmly adherent, rather thick, gray scales. When removed, the scales often present on their under surface projections that fit into minute depressions in the cutis, in which bleeding points may be seen. Usually more than one lesion is present. The lesions may develop into cornu cutaneum. The presence of inflammation is to be regarded with suspicion, as it usually indicates malignant change (fig. 1).

Verruca senilis occurs by predilection on the trunk, particularly in the seborrheic areas. Like keratoma senilis, the lesions are usually multiple, and occur in elderly persons. When fully developed, the lesions consist of sharply circumscribed, round or oval, elevated, yellow or brown patches, often appearing as though "stuck on" the skin, and covered with rather thin, greasy scales. They begin as small, light

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* Abridgment of thesis submitted to the faculty of the Graduate School of the University of Minnesota, in partial fulfilment of the requirements for the degree of Master of Science in Dermatology and Syphilology.

Fig. 1.—Keratoma senilis with cornu cutanem.

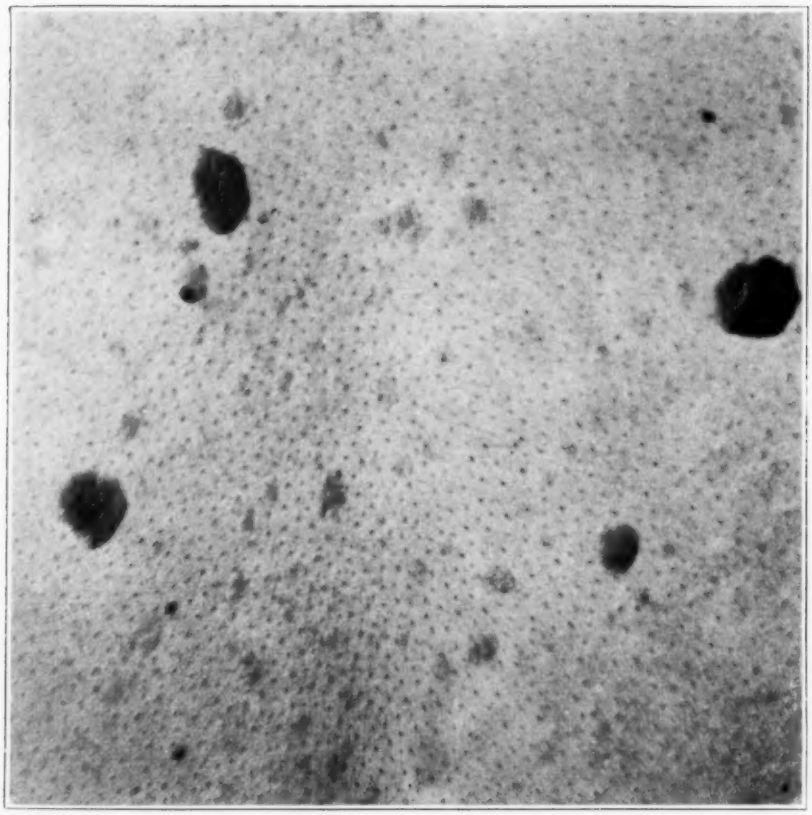

Fig. 2.—Verruca senilis of the back, with lesions in various stages of development. Associated vascular ectasias may be noted.

yellow macules, which gradually increase in size and become deeply pigmented, so that many are deep brown or black when fully developed. They are often granular, owing to the presence of numerous minute, light colored spots on the surface, which represent the sites of small keratoid plugs. Inflammatory reaction at the base and subjective symptoms are not common (fig. 2).

REVIEW OF THE LITERATURE

The earliest textbooks on dermatology do not include descriptions of keratoma senilis or verruca senilis, and it was not until the latter part of the nineteenth century that descriptions began to appear in the literature under various names (Barthélemy,[1] Handford[2] and Neumann[3]). Pollitzer,[4] in 1890, published the first detailed description of seborrheic wart. Unna[5] concluded that seborrheic nevi (verruca senilis) were true soft nevi, differing from the latter only in the content of fat. Dubreuilh[6] was the first to point out the significance of distinguishing keratoma senilis from verruca senilis because of the tendency of the former to undergo malignant change. Hartzell[7] and Schuchardt[8] were of the opinion that the sweat glands played an important part in the production of keratoma senilis.

Dubreuilh,[9] in 1904, described typical verruca senilis, but could not confirm Pollitzer's observations regarding the presence of fat in the lesion. In the English textbooks, Hyde,[10] Hartzell[11] and Ormsby[12] referred to Pollitzer for the pathologic description of verruca senilis.

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1. Barthélemy, M.: Des verrues séborrhéiques ou verrues plates de la vieillesse, Ann. de dermat. et syph. **12**:535, 1881.

2. Handford, quoted by Pollitzer (footnote 4).

3. Neumann, quoted by Pollitzer (footnote 4).

4. Pollitzer, S.: The Seborrhoeic Wart, Brit. J. Dermat. **2**:199 (July) 1890.

5. Unna, P. G.: Hard and Mixed Nevi; Naevi Seborrheica, in Histopathology of Diseases of the Skin, New York, The Macmillan Company, 1896, pp. 1140 and 1164.

6. Dubreuilh, W.: Des hyperkératoses circonscrites, Ann. de dermat. et syph. **27**:1158, 1896.

7. Hartzell, M. B.: Some Precancerous Affections of the Skin, More Particularly Precancerous Keratoses, J. Cutan. Dis. **21**:393 (Sept.) 1903.

8. Schuchart, quoted by Hartzell (footnote 7).

9. Dubreuilh, W. A.: Verrue sénile, in La pratique dermatologique, Paris, Masson et Cie, 1904, vol. 4, p. 828.

10. Hyde, J. N.: Keratosis Senilis; Verruca Senilis Vel Plana, in Diseases of the Skin, Philadelphia, Lea & Febiger, 1909, pp. 457 and 483.

11. Hartzell, M. B.: Keratoma Senilis; Verruca Senilis, in Diseases of the Skin, Philadelphia, J. B. Lippincott & Company, 1914, pp. 472 and 500.

12. Ormsby, O. S.: Keratosis Senilis; Verruca Senilis, in Diseases of the Skin, Philadelphia, Lea & Febiger, 1927, pp. 474 and 504.

DuBois,[13] in 1914, described in detail what he thought was a new and unique type of pigmented nevus of the sebaceous gland, but which in reality was a typical verruca senilis. D. W. Montgomery [14] described keratoma senilis under the term seborrheic wart and, in an earlier article, as senile patches. Williams [15] said: "I have never been able to convince myself that there is any essential difference between this lesion (keratoma senilis) and the seborrheic wart." Sutton [16] and MacKee [17] described three types of lesions as seborrheic keratosis, which they regarded as precancerous. Sequeira [18] distinguished keratoma senilis from verruca senilis, and like Darier and Pollitzer,[19] was of the opinion that the former was obviously precancerous. Highman [20] described both lesions under the name seborrheal keratoma and stated that a small proportion proceeds to the formation of basal or squamous cell epithelioma. Darier [21] stated: "The clinical characteristics, the structure and the location, all distinguish the verruca senilis from the keratoma senilis, with which they are too often confused."

The most detailed description of keratoma senilis and verruca senilis was given by Freudenthal,[22] with whose observations Gans [23] was in agreement. He concluded that keratoma senilis is precancerous and that verruca senilis is not precancerous. In Freudenthal's opinion, neither Pollitzer's description of the seborrheic wart nor Unna's description of

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13. DuBois, C.: Étude histologique d'un lentigo, Ann. de dermat. et syph. **45**:385, 1914-1915.

14. Montgomery, D. W.: The Anatomy of a Patch of Seborrhoeic Keratosis, J. Cutan. Dis. **32**:6 (Jan.) 1914; A Contribution to the Treatment of Senile Patches, Philadelphia M. J. **1**:211 (Jan. 29) 1898.

15. Williams, C. M.: Malignant Degeneration in Benign Dermatoses, Arch. Dermat. & Syph. **2**:168 (Aug.) 1920.

16. Sutton, R. L.: The Symptomatology and Treatment of Seborrheic Keratoses, J. A. M. A. **64**:403 (Jan. 30) 1915.

17. MacKee, G. M., and Lewis, G. M.: Precancerous Dermatoses, Atlantic M. J. **31**:371 (March) 1927.

18. Sequeira, J. H.: Verruca Plana Senilis, "Seborrhoic" Wart; Keratosis Senilis, in Diseases of the Skin, ed. 3, Philadelphia, P. Blakiston's Son & Company, 1919, pp. 523 and 524.

19. Darier, J., and Pollitzer, S.: Flat Senile Warts (Verruca Plana Senilis); Keratosis Senilis, in a Textbook of Dermatology, Philadelphia, Lea & Febiger, 1920, pp. 208-209.

20. Highman, W. J.: Seborrhoeal Keratomas, in Dermatology, New York, The Macmillan Company, 1921, p. 333.

21. Darier, J.: Verrues planes senilis, in Précis de dermatologie, ed. 4, Paris, Masson et Cie, 1928, p. 263.

22. Freudenthal, Walter: Verruca senilis und Keratoma senilis, Arch. f. Dermat. u. Syph. **152**:505, 1926; Rumpfhautepitheliom nebst Bemerkungen über die Verruca senilis und das Keratoma senilis, ibid. **158**:539, 1929.

23. Gans, Oscar: Keratoma senilis; Verruca senilis, Histologie der Hautkrankheiten, Berlin, Julius Springer, 1928, vol. 2, pp. 374 and 377.

soft nevi could be regarded as typical of verruca senilis. Eller [24] concluded that: (1) the two are distinct disease entities, often difficult to distinguish when occurring together on the face; (2) keratoma senilis is a misnomer; (3) it is distinctly precancerous, and when epithelioma develops, it is always of the prickle cell variety, and (4) seborrheic keratosis on the face may undergo malignant change, thus giving rise to epithelioma of the basal cell type.

KERATOMA SENILIS

For the study of the lesions in keratoma senilis, pathologic material was obtained from thirty-one cases seen at the Mayo Clinic.

The ages of the patients presenting lesions diagnosed as keratoma senilis varied from 32 to 77 years, the average age being 58 years. Twelve of the thirty-one patients were women, and nineteen were men. Most of them were between the ages of 50 and 70 years. The duration of the disease varied from three months to sixteen years. Sixteen lesions were on the trunk, but since lesions on the face are commonly treated by methods other than excision, this percentage is higher than usual. Malignant change occurred in eight cases.

Histopathology.—Lesions of keratoma senilis may present marked or slight hyperkeratosis. The horny lamellae may be loosely arranged or compact. A verrucous outline is common. Parakeratosis may or may not be present. Freudenthal found hyperkeratosis and parakeratosis alternating, the former always at the site of a sweat duct or hair follicle. I found this condition only in one or two instances.

Acanthosis is irregular. The rete ridges may be long and thin or short and wide. Occasionally cystlike spaces are present, similar to those seen in verruca senilis. Changes in the staining reactions of the cells are common; groups of cells here and there will stain lighter with hematoxylin than the surrounding cells. At the orifices of the sweat duct a triangular shaped area, its base directed toward the surface, in which the cells stain deeply, occasionally is seen (fig. 3*a*). The individual cell changes, however, are more significant. Mitotic division of cells is commonly seen. Division by amitosis apparently also takes place, which leads to the production of giant cells with multiple, clumped nuclei. These cells are from eight to ten times larger than the normal prickle cell and contain several nuclei which are grouped usually toward one side of the cell body. Outside the nuclei is a clear zone, which is surrounded by a zone of protoplasm. Intercellular communications are retained (fig. 3*b*). Another common type of giant epithelial cell has one large nucleus with granular chromatin and one

24. Eller, J. J., and Ryan, V. J.: Senile Keratosis and Seborrheic Keratosis, unpublished data.

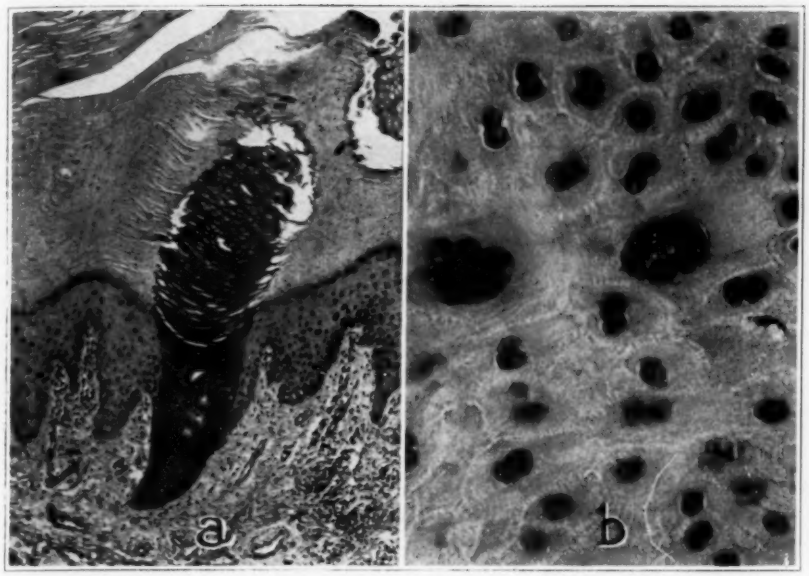

Fig. 3.—Keratoma senilis. In *a* is seen altered staining reaction of the cells about the sweat duct, with parakeratosis stopping abruptly at the orifice of the duct; × 50. Multinucleated giant cells are shown in *b;* × 400

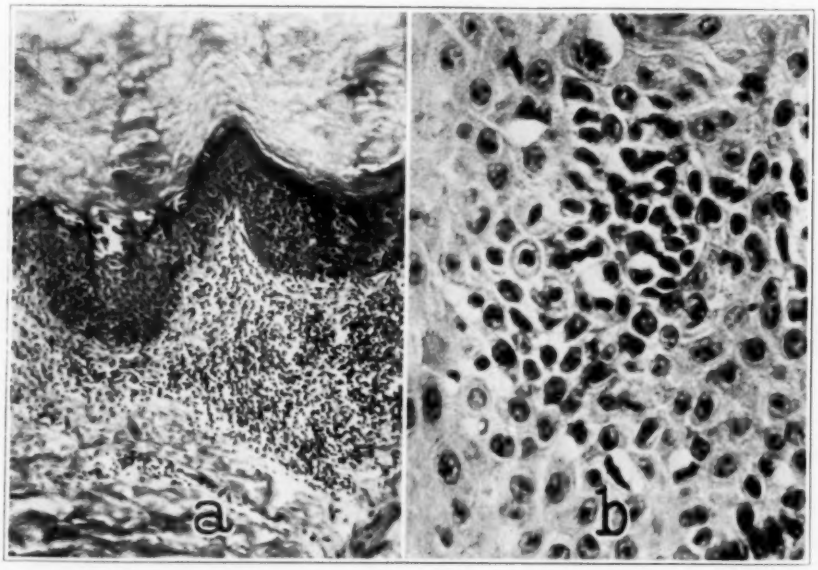

Fig. 4.—Keratoma senilis. In *a* are seen hyperkeratosis, "corps ronds" and "grains" with inflammatory reaction in the cutis; × 75. In *b,* dyskeratotic cells and intracellular and intercellular edema are seen; × 50.

or more nucleoli. The "dyskeratotic cells," as recently defined by Darier,[25] are similar to those seen in Bowen's disease and are a characteristic part of the microscopic picture (fig. 4*a* and *b*). Intercellular and intracellular edema accompany these changes, at times producing true spongiosa. The basal cell layer, although usually intact, may be involved in the underlying edematous process to the extent of the formation of liquefaction necrosis and occasionally of true "Lucken." Pigment, if present, is found particularly in the dendritic cells of the epidermis.

An inflammatory reaction is present in the skin, as manifested by edema of the papillary layer and the upper layer of the skin, by dilatation of the vessels and by a perivascular infiltrate of lymphocytes and a few plasma cells. The degree of inflammatory reaction varies in different lesions. In the areas in which the inflammatory infiltrate occurs, the elastic fibers are disintegrated or entirely absent. Homogenization of elastic and connective tissue fibers and the formation of "kollacin," characteristic of senile degenerative changes, may be noted in some cases. This is incidental and is dependent on the site of the lesion and the age of the patient. Mucin was not found. The hair follicles, sebaceous glands, sweat glands and ducts did not present changes of note.

VERRUCA SENILIS

Pathologic material was obtained for the study of the lesions of verruca senilis from fifty-two cases seen at the Mayo Clinic. Twenty-four of the patients were women, and twenty-eight were men. Their ages varied from 22 to 72 years, the average being 52 years. Most of the patients were seen between the ages of 40 and 70. The duration of the lesions varied from two to sixty years, but in many cases was not definitely known. The lesions were situated predominantly on the trunk; only five were on the face. In most cases, the lesions were associated with other types of nevi, particularly of the vascular type. Malignant changes were not found.

Histopathology.—There are two main types of verruca senilis, in one of which hyperkeratosis is the striking feature and in the other acanthosis makes up the bulk of the lesion. The second type is more common.

The first type is characterized by marked, irregular hyperkeratosis and usually by a verrucous outline (fig. 5*a*). The stratum corneum has a tendency to dip and form deep, irregular, hyperkeratotic crypts.

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25. Darier, J.: Note sur la dyskératose, en particulier dans la "maladie de Paget," Bull. Soc. franç. de dermat. et syph. **32**:1 (Jan. 18) 1925; Dyskératose folliculaire, in Précis de dermatologie, ed. 4, Paris, Masson et Cie, 1928, p. 263.

Some of these occur at the orifices of hair follicles and sweat ducts. Irregular acanthosis is also present. The normal relationship of rete ridges to papillae is disturbed, the latter at times being long and thin and forming filiform projections. In other cases, the rete ridges enlarge in all dimensions at the expense of the papillae, forming large, solid epidermal masses, containing here and there characteristic horny cysts. Many cells seem a little smaller and more deeply stained than normal, and intercellular and intracellular edema may distort the outline of the cells, but dyskeratotic changes are not seen in the individual cells. Occasionally, a mitotic figure is seen. The basal cell layer is intact.

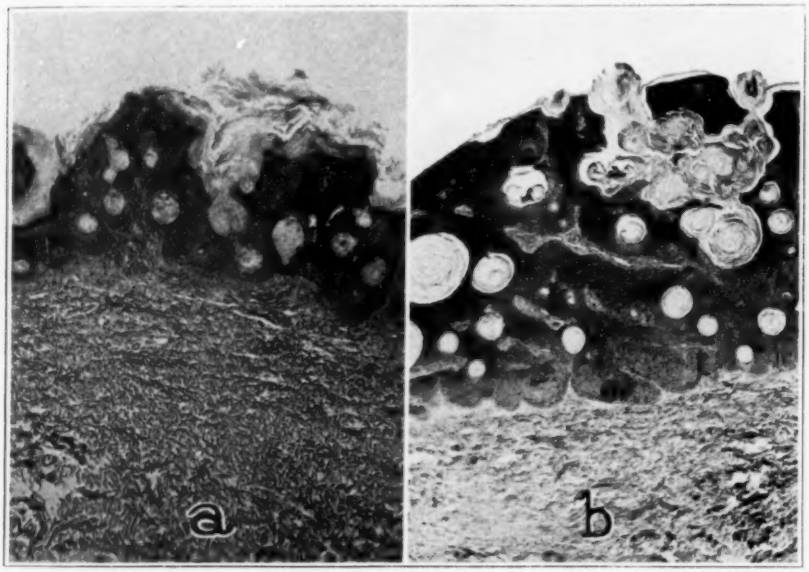

Fig. 5.—Verruca senilis. The verrucous type showing hyperkeratosis, irregular acanthosis and horny cysts is shown in *a;* × 15. The acanthotic, solid type, showing branching hyperkeratotic crypts and horny cysts is shown in *b;* × 15.

Pigmentation is so constant that it becomes characteristic. The pigment is melanin, as is shown by staining with silver nitrate and hematoxylin. It is found in the chromatophores of the cutis, in and between the basal and prickle cells and in the stratum corneum. In the chromatophores, the pigment granules are rather large and coarse, and at times so dense as to mask the outline of the cell. In the epidermal cells the pigment granules are fine and regular in size. Few dendritic cells are found, the bulk of pigment being in the palisade basal cells. The amount of pigment varies markedly in different lesions and is not as marked in the verrucous type as in the others.

The second type of lesion is characterized by marked acanthosis. The stratum corneum over the surface of the lesion may not be thicker than that over the adjacent normal epidermis. Numerous, deep, irregular, branching hyperkeratotic crypts dip down into the substance of the lesion. The bulk of the lesion is made up of the extremely irregular hyperplasia of the prickle cells, the character of which allows further subdivision into a solid and a loose network type (fig. 5*a* and 6*a*). When the rete ridges increase in size in all dimensions, the solid type is produced. Partial fusion of the rete ridges takes place to form an epidermal network, in the meshes of which are islands of connective

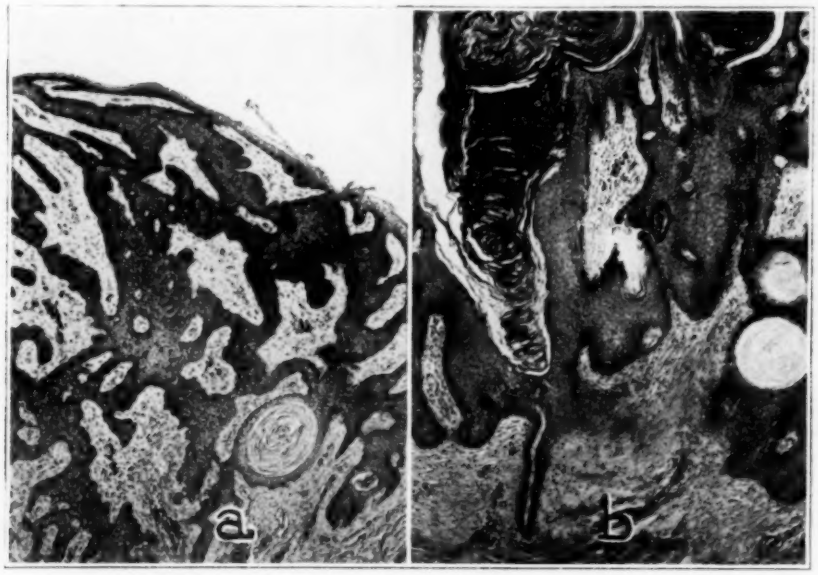

Fig. 6.—Verruca senilis. The acanthotic, loose network type with marked pigmentation is shown in *a*. There is a resemblance to epithelioma adenoides cysticum; × 35. In *b*, the sweat glands are shown unaltered until the stratum corneum is reached. Increased pigmentation appears in the basal cell layer; × 45.

tissue which represent the papillary bodies. When the rete ridges increase in length but not in width, the network is composed of narrow epidermal cords and large islands of connective tissue. In the epidermis are found many cystlike spaces filled with hyperkeratotic material and bordered by stratum granulosum; these spaces are characteristic of verruca senilis, and their significance has not been generally understood. Study of serial sections reveals that they are not produced by dilatation of sweat ducts or hair follicles. The number of follicles and ducts seen in any given section is small and could not account for the large number of cysts present. The hyperkeratotic crypts which dip

down from the surface of the lesion are complex, irregular and branching. The branches are surrounded by the acanthotic stratum malpighii, and, on sectioning, many are cut obliquely or across which gives the appearance of isolated cysts. In the same way, the papillary bodies, which are also branched and irregular, are cut to produce the effect of isolated islands of connective tissue.

With the differences noted, all lesions of verruca senilis are similar in nature. In the cutis there is occasionally an inflammatory reaction of varying degree of intensity; the hair follicles, sebaceous glands, sweat glands and ducts are normal. In the epidermis near the stratum corneum, the hair follicles and sweat ducts become dilated and plugged with hyperkeratotic stratum corneum, and thus contribute to some extent to the keratotic crypts and horny cysts (fig. *6b*).

DIFFERENTIAL DIAGNOSIS

Clinically, keratoma senilis and verruca senilis are usually readily distinguished from each other and from other forms of dermatosis when occurring either on the trunk or on the face. Microscopically, the dyskeratotic cells, together with the other changes in the prickle cell layer and the relative absence of pigment, serve to distinguish keratoma senilis from verruca senilis. Keratoma senilis must sometimes be distinguished from lupus erythematosus, superficial epitheliomatosus, Bowen's disease, seborrheic dermatitis and epithelioma. In one case (fig. *7b*) included in this series, one area microscopically resembled Darier's disease,[25] but other areas were typical keratoma senilis. Verruca senilis is most often confused with the common pigmented nevi. The nevoid melano-epithelioma of Bloch [26] must also be differentiated. I believe that Becker's [27] benign melanoma (case 1) is a case of verruca senilis. Microscopically, dermatosis papulosa nigra [28] is distinguished from verruca senilis by the presence of rudimentary hair follicles and sebaceous glands. Granuloma senile [29] apparently represents verruca senilis with secondary inflammatory reaction, simulating granuloma pyogenicum.

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26. Bloch, B.: Ueber benigne, nicht naevoide Melanoepithelioma der Haut nebst Bemerkungen über das Wesen und die Genese der Dendritenzellen, Arch. f. Dermat. u. Syph. **153**:20, 1927.

27. Becker, S. W.: Cutaneous Melanoma, Arch. Dermat. & Syph. **21**:818 (May) 1930.

28. Michael, J. C., and Seale, E. R.: Dermatosis Papulosa Nigra, Arch. Dermat. & Syph. **20**:629 (Nov.) 1929; **21**:295 (May) 1930.

29. Johnson, C. E., and Harvey, S. C.: Granuloma Senilis, Arch. Dermat. & Syph. **21**:566 (April) 1930. Kreibich, C.: Granuloma Senile, Arch. f. Dermat. u. Syph. **153**:807, 1927.

ETIOLOGY

Changes in the skin with advancing age and exposure to the sun and wind have been regarded as etiologic factors in keratoma senilis.[30] Dubreuilh [31] and Darier [32] expressed the belief that hereditary predisposition of the skin might also be added. These lesions are not common in persons of the true brunette type and infrequent among members of the dark-skinned races, probably because of the protection afforded by the pigment in the skin. The microscopic picture does not suggest an additional etiologic factor. The biologic and biochemical problems inferred are worthy of further study.

Microscopic study will not support the contention, long held, that verruca senilis is concerned with alteration of either the sebaceous or sudoriparous apparatus. Darier [21] expressed the idea that it belonged in the group of delayed nevi. Dawson,[33] in a recent paper, described typical verruca senilis under the classification of "acanthotic pigmented nevi of the epidermal layer." He felt that the absence of nevus cells was explained on the supposition that although the stimulus to proliferation of the pigment-producing cells was present, it was not sufficient to lead to detachment of the cells from the epidermis. I believe that verruca senilis should be regarded as a delayed nevus of the epithelial type.

RELATION TO OTHER PRECANCEROUS LESIONS

Among the group of lesions designated as precancerous dermatosis, keratoma senilis bears the closest resemblance to Bowen's [34] disease. In spite of the objections to the use of the term "precancerous" voiced by Heimann,[35] Drake and Whitfield,[36] Fraser,[37] Kogoj [38] and others,

30. Engman, M. F.: Precancerous Conditions of the Skin, J. Lab. & Clin. Med. **1**:31, 1915. McCoy, J. N.: Solar Keratoses and Cutaneous Cancer, Arch. Dermat. & Syph. **1**:175 (Feb.) 1920. Montgomery, D. W.: Unusual Exposure to Light Followed by Seborrheic Keratosis, J. A. M. A. **60**:709 (Jan. 4) 1913.

31. Dubreuilh, W.: Epithéliomatose d'origine solaire, Ann. de dermat. et syph. **38**:387, 1907.

32. Darier, J.: Keratoma senilis, in Précis de dermatologie, ed. 4, Paris, Masson et Cie, 1928, p. 992.

33. Dawson, J. W.: Melanomata, Their Morphology and Histogenesis: Study of Cell Origins and Transformations with Critical Discussion on Aspects of Tumour, Growth and Clinical Review, Edinburgh M. J. **32**:501 (Oct.) 1925.

34. Bowen, J. T.: Precancerous Dermatoses: A Study of Two Cases of Chronic Atypical Epithelial Proliferation, J. Cutan. Dis. **30**:241 (May) 1912.

35. Heimann, W. J.: Precancerous Dermatoses, J. Cancer Research **1**:343 (July) 1916.

36. Drake, J. A., and Whitfield, Arthur: Paget's Disease of the Vulva, Brit. J. Dermat. **41**:177 (May) 1929.

37. Fraser, J. F.: Bowen's Disease and Paget's Disease of the Nipple: Their Relation to Dyskeratosis, Arch. Dermat. & Syph. **18**:809 (Dec.) 1928.

38. Kogoj, F.: La dyskératose, Ann. de dermat. et syph. **8**:351, 1927.

it would seem that it should be retained, if by it is meant that a lesion is potentially carcinomatous. H. Montgomery [39] advocated retaining the term "precancerous dermatosis of Bowen" in a restricted sense when the lesion corresponds clinically to the descriptions of Bowen [40] and Darier,[41] and microscopically shows the structure described by Bowen with the basal cell layer intact. There was one case in the present series which on clinical examination was found to be typical keratoma senilis, but which on microscopic examination presented all the features of Bowen's disease (fig. 7*a*).

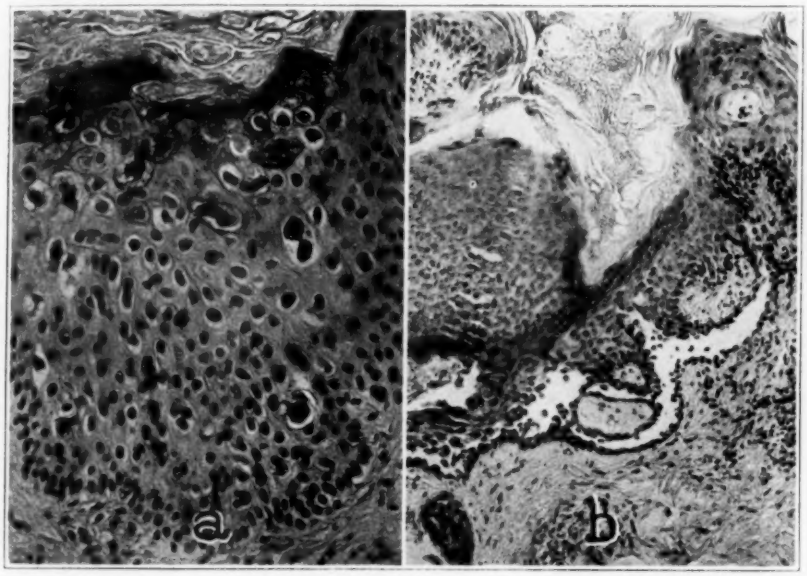

Fig. 7.—Keratoma senilis. The section in *a* resembles Bowen's disease. Multinucleated cells, mitosis and dyskeratotic cells are shown; × 175. In *b*, there is a resemblance to Darier's disease; elsewhere the picture was that of keratoma senilis and clinically the lesion was typical; × 100.

The other lesions of this group, namely, those of Paget's disease, roentgen-ray dermatitis and keratosis, xeroderma pigmentosum and arsenical keratosis are distinguished by their concomitant features.

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39. Montgomery, Hamilton: Superficial Epitheliomatosis, Arch. Dermat. & Syph. **20**:339 (Sept.) 1929.

40. Bowen, J. T.: Precancerous Dermatoses: A Sixth Case of a Type Recently Described, J. Cutan. Dis. **33**:787 (Dec.) 1915.

41. Darier, J.: La dermatose précancéreuse de Bowen dyskératose lenticulaire et en disques, Ann. de dermat. et syph. **45**:449, 1914-1915.

EPITHELIOMATOUS METAMORPHOSIS

The microscopic picture of keratoma senilis suggests the possibility of further evolutionary changes of malignant character. A few lesions become malignant, but exact statistics are not available. In eight cases (25 per cent of this series), malignant change was noted. This is an unusually large percentage, but the percentage is of cases, not of total lesions. One of the eight cases was a case of the basal squamous cell variety recently described by H. Montgomery,[42] one was of the basal cell type (fig. 8), and six were squamous cell epitheliomas, four of

Fig. 8.—Basal cell epithelioma arising from a keratoma senilis of the back.

which were graded 1, and two were graded 2, according to Broders'[43] grading.

Malignancy arising from keratoma senilis is usually of the squamous cell, rather than of the basal cell type. The mechanism of the development of malignancy in these lesions is similar to that seen in Bowen's disease, namely, a result of the dyskeratotic phenomena.

Verruca senilis is not a precancerous lesion. Superficially, the microscopic picture at times resembles that of epithelioma adenoides cysticum. I cannot agree with Eller that verruca senilis on the face

42. Montgomery, Hamilton: Basal Squamous Cell Epithelioma, Arch. Dermat. & Syph. **18**:50 (July) 1928.

43. Broders, A. C.: The Grading of Carcinoma, Minnesota Med. **8**:726 (Dec.) 1925.

not uncommonly gives rise to basal cell epithelioma. That malignancy would never occur, however, I should hesitate to say. The lesion is essentially epithelial hyperplasia, and it is entirely conceivable that under proper stimulus, such as continued irritation, it might lose its benign characteristics.

SUMMARY AND CONCLUSIONS

Keratoma senilis (senile keratosis) and verruca senilis (seborrheic keratosis) are distinct clinical and pathologic entities, a fact that is not clearly established in the literature.

Keratoma senilis is characterized by hyperkeratosis, irregular acanthosis with dyskeratotic phenomena and secondary inflammatory reaction. Verruca senilis is characterized by hyperkeratosis, irregular acanthosis with the formation of an epithelial network, absence of dyskeratosis, a mild inflammatory reaction and usually increased pigmentation.

Although the term keratoma senilis is open to objections, it has the advantage of recalling two of the characteristics of the lesion, namely, the hyperkeratosis and the age of the patient. The term verruca senilis is preferable to that of seborrheic keratosis, since there is no pathologic basis for the use of the latter. Both types of lesions may occur either on the exposed or on the covered surfaces of the body.

Keratoma senilis appears later in life, in most instances, than verruca senilis.

The use of the term precancerous as meaning potentially cancerous is justified with reference to keratoma senilis. There is an apparent relationship between this lesion and Bowen's disease. Both are characterized by dyskeratotic phenomena.

Epitheliomas arising from keratoma senilis are usually, but not always, of the squamous cell variety. The etiology is probably the interaction of exposure or senile changes with some inherent peculiarity of the epidermis. Verruca senilis is not a precancerous lesion. It is a benign epidermal hyperplasia, probably best classified with delayed epithelial nevi. Because of the difference in prognosis, differential diagnosis is important.

News and Comment

SECTION ON DERMATOLOGY, AMERICAN MEDICAL ASSOCIATION

Members of the Section on Dermatology of the American Medical Association are invited to be guests of the Philadelphia Dermatological Society at a Luncheon to be given on Wednesday, June 10, at 12:30 p. m., at the University Club, 16th and Locust Streets, Philadelphia.

Editorial

WHAT AN EDITOR LIKES TO GET IN A MANUSCRIPT

Of course the first thing an editor likes to get is a record of good original work; the next thing, is a paper that is well written and in readable form. One of the things that make an editor love an author is a paper that indicates a sense of responsibility for authorship; that he has taken the trouble to plan and develop it in logical sequence, and that he knows that good manners in writing require attention to spelling, grammar and punctuation. The writer who takes it for granted that the editor realizes that he can spell, punctuate and write grammatical English and so does not take the trouble to do so may have a fine indifference, but he has not specialized in knowledge of human nature. Editors are apt to be irritable, like other people, and to feel that it is not their place to labor over the corrections that an author should make for himself. Believe it or not, editors are weak, are impressed by externals and are likely to overlook the nugget of gold in the author's package if the package is one in which only a witch would expect gold and only a hero would take the trouble to find it.

There are some other details that, judging from personal experience, make an editor responsive and more appreciative of a paper. Double spacing and wide margins appeal to the editor's eye; they give him the space to make comments and corrections which indicate his editorial competency. The charm of a Wordsworth sonnet would very likely be overlooked by a tired editor if the manuscript was single spaced and full of corrections in longhand—certainly if in poor longhand. Clean manuscripts make a good impression. It is well to start with a neat manuscript, because it will be careless looking enough after the editor has covered it with pencil marks. Use regular business letter paper; and, so far as this particular editor is concerned, he is not made any happier by having the pages fastened together or bound between covers that have to be taken off before he can read the paper easily. The less unnecessary garnishing there is with the meat, the better he likes it.

Do not send more illustrations and tables than you feel are necessary. Do not repeat in the tables what is in the text. Tables and illustrations are expensive to reproduce, and, in a sense, the answer is still true that the country editor gave when the thrilled young lady asked him what was the most interesting thing an editor had to do, and he

replied, "Pay the hands." Cost must be considered even by the most generous and irresponsible of editors. Put the author's name on illustrations and tables; otherwise, even if they do not get lost, they are apt to cause a good deal of trouble.[1] If you send more illustrations or tables than your conscience justifies, don't ask the editor to pick out the ones to be published. That usually means revising the manuscript, and it is not the editor's job anyway. Put the legends for your illustrations at the end of the paper; that is most convenient for the printer.

It is only fair that an editor should acknowledge the receipt of a paper, and he has no right to get in a bad humor if the writer should inquire in a reasonable time whether the paper has been received and accepted. But do not press for early publication unless you have some valid reason for asking preference for your paper. Papers accumulate far ahead, particularly just after annual meetings, so that delay in publication is inevitable. The editor, as a rule, is not playing favorites, and he tries to make up each number as he thinks best, without regard to individuals; so if you are inclined to become impatient with him, not to say in very bad humor, remember the notice in the concert hall, "Don't shoot the fiddler; he is dong the best he can." And try to believe that the editor will give you as good a break as anybody, and that it is probable that your paper should not be pushed ahead of most of those already on hand. Remember what you think of the fellow who tries to break into the ticket line out of turn. On the other hand, if you believe that you have reasons for asking publication out of turn—reasons that would justify it in the minds of those whom you are displacing—the editor will probably give them consideration if you bring them to his attention. In this connection, remember that all of us are inclined to overestimate the importance of our particular baby.

There are also some very, very little things that influence the editor. A stamped envelop for return of the mansuscript in case it is not accepted—or, as the editor says with the politeness for which editors are famous, "is returned with great regret because of circumstances over which he has no control"—indicates a sort of modesty that predisposes the editor in favor of the author.

The letter of transmission signed by the author is appealing; if it is signed by the secretary or has that old, but now happily disappearing evidence of excessive value of the busy man's time, "Signed but not read by the writer," the editor is likely to have the feeling that if he must take the time to wade through the thing the author might

1. The American Medical Association is glad to supply labels for this purpose on request.

at least have taken the time to read his letter and to sign it; it is no treat to the editor, either. Editors like to be flattered just like other people.

These thoughts are not aimed at anybody. They are vagrant ideas that have accumulated in the course of experience. Editors get the impression that authors like to have their papers accepted, and if this particular editor could do anything to conduce to the happiness of the authors who submit papers by giving suggestions that would make acceptance more likely, he would feel that he had been of some service to an important, if small, fraction of society. That is the high purpose which animates this editorial.

W. A. P.

CORRECTION

In the article by Dr. E. William Abramowitz in the April issue (ARCH. DERM. & SYPH. **23**:644, 1931) the following errors occurred:

Page 651—13th line, "boric acid" should read "benzoic acid."

Page 661—In the last formula, near the bottom of the page, "National Formulary" following Lotio Alba should read "Pharmaceutical Recipe Book."

Page 669—The formula appearing about the middle of the page should begin:

	Gm. or Cc.
Coal tar Solution[6]	5
Glycerin or castor oil	5
Etc.	

Page 673—Lines 10 and 11, should read 3 per cent salicylic acid, 5 per cent benzoic acid in one hundred parts of petrolatum.

In the paper by Dr. Samuel M. Peck, entitled, "The Melanotic Pigment in the Skin, Hair and Eye of the Gray Rabbit: Its Embryologic Development and the Question of the Mesodermal Origin of Epidermal Melanoblasts," in the April issue (ARCH. DERM. & SYPH. **23**:705, 1931), the second sentence in the second paragraph on page 711 should read: "Sections 20 to 30 microns thick are placed in a 0.1 per cent solution," instead of in a 1 per cent solution.

Abstracts from Current Literature

EDITED BY HERBERT RATTNER

TREATMENT OF CHOREA WITH PHENYL-ETHYL-HYDANTOIN. J. D. PILCHER and H. J. GERSTENBERGER, Am. J. Dis. Child. **40**:1239 (Dec.) 1930.

In the treatment of children with chorea by phenyl-ethyl-hydantoin the majority react with fever (from 102.2 to 104 F.) and a generalized exanthem. The latter usually appears at the height of the fever and commonly is morbilliform, similar to that following the administration of phenobarbital. It occurs on the face, trunk and extremities. Less frequently it resembles the rash of scarlet fever and in rare cases it is urticarial. As a rule, the exanthem is associated with fever, but either symptom may occur without the other. Less common complications include stomatitis, irritation of the mucous membranes, vulvovaginitis and balanitis. Slight edema of the face may precede the appearance of the rash. Improvement was noted only in those patients who reacted with fever and rash, and the improvement seemed to start about the time the rash appeared.

ANDERSON, Los Angeles.

CANCER. Ann. Surg., January, 1931, vol. 93, no. 1.

This number of the *Annals of Surgery* is composed of international contributions to the study of cancer in honor of James Ewing. In addition to appropriate biographical and laudatory articles concerning Dr. Ewing and his work, the volume is divided into four parts. These deal with: (1) cancer in its general relations; (2) cancer research; (3) regional cancer; (4) radium and roentgen therapy for cancer. As the articles are too numerous to permit a review of each one and many are of limited interest to the dermatologist, a brief review of those most appropriate to this field follows.

SUSCEPTIBILITY TO CANCER. W. J. MAYO, Ann. Surg. **93**:16 (Jan.) 1931.

The relation of cancer to age is recognized, and the reputed increase of cancer may be due to larger numbers of persons reaching the cancer age. Susceptibility of organs is well known, that is, the genitalia and breasts in women and the stomach, mouth and urinary apparatus in men. Instances of production of susceptibility through chronic irritation are quoted. Experimental work with mice has shown variation in individual susceptibility, this factor being increased through inbreeding of nonsusceptible strains. Work of other authors on which hope is based for the ultimate ability to increase individual resistance to cancer is quoted.

RESISTANCE AND SUSCEPTIBILITY TO CANCER. W. CRAMER, Ann. Surg. **93**:20 (Jan.) 1931.

An experimental analysis of the process of carcinogenesis shows that it is one that does not arise merely as the result of direct action of a carcinogenic agent on epithelial cells, but is a much more complex one. In one sense, it emphasizes the local origin of the disease, for even if a large area of epithelial cells is subjected to chronic irritation, cancer arises only in a very small portion. In another sense, it widens this conception by showing that the local development of malignancy is influenced by factors that do not reside in the epithelial cells, but in the organism, and exert their influence presumably through the mesenchymal cell system. Study of these factors may enable modification of their activity to delay or even prevent the onset of cancer.

HEREDITY AND CANCER. H. T. DEELMAN, Ann. Surg. **93**:30 (Jan.) 1931.

The author found that in a series of families of patients with cancer, cancer is found more frequently than in any other series of families; the surplus of cancer in the family of patients with cancer always accumulates in certain distinct families. There is a large group of patients with cancer in whose family cancer is no more frequent than in the average population. Hereditary influences are evident only in a small category of cases of cancer.

CANCER AND SMOKING HABITS. FREDERICK L. HOFFMAN, Ann. Surg. **93**:50 (Jan.) 1931.

From statistics of life insurance companies the author found that smoking habits unquestionably increase the liability to cancer of the mouth, throat, esophagus, larynx and lungs. Syphilis and dental defects are complicating factors, in the absence of which smoking habits are less injurious. Increase in cancer of the lungs is probably to some extent due to the increasing inhalation of smoke from cigarets.

EPIDERMOID CARCINOMA IN SEBACEOUS CYSTS. EVERETT L. BISHOP, Ann. Surg. **93**:109 (Jan.) 1931.

The author examined 119 cysts and keratomas microscopically, of which 11 showed definite carcinoma and 2 premalignant changes. The average age of all of the patients was 38.3 years; of those with malignant conditions, 64.2 years. Only one case was diagnosed as malignant at the time of admission. There was no difference in the incidence of sex. The scalp and face were most commonly affected.

THE GENETIC NEOPLASTIC RELATIONSHIPS OF HODGKIN'S DISEASE, ALEUKEMIC AND LEUKEMIC LYMPHOBLASTOMA, AND MYCOSIS FUNGOIDES. ALDRED S. WARTHIN, Ann. Surg. **93**:153 (Jan.) 1931.

On the basis of a histopathologic analysis of 506 cases, the author found that Hodgkin's disease, sarcomatous Hodgkin's disease, aleukemic and leukemic lymphoblastoma and aleukemic and leukemic mycosis fungoides are true neoplasms and are genetically closely related. Transition forms exist between all types. The cellular origins, age incidences and clinical features are considered. Analogies and differences between these and infectious diseases are discussed, with a preponderance of evidence in favor of all being malignant.

SUSCEPTIBILITY AND RESISTANCE TO TAR CANCER. J. MAISIN, Ann. Surg. **93**:180 (Jan.) 1931.

From his experiments with mice, the author found that cancer caused by tar is the result of a local irritation plus a general intoxication. Magnesium and copper salts are capable of delaying the appearance of cancer and of lowering the percentage of induced tumors. Salts of radio-active metals have the opposite effect. A diet of liver activates the development of cancer caused by tar. Vitamin A, when absorbed, in addition to a normal alimentation, has no inhibitive effect on the appearance of cancer. Preceding the development of cancer caused by tar and during its evolution, the metabolism of fats is deficient and the variations of the cholesteremia are marked.

EXPERIMENTS AND CLINICAL STUDIES ON THE TREATMENT OF CANCER BY DICHLORETHYL-SULPHIDE (MUSTARD GAS). FRANK E. ADAIR and HALSEY J. BAGG, Ann. Surg. **93**:190 (Jan.) 1931.

In this article the authors review the results of treatment by application of mustard gas to various types of cutaneous malignant conditions in twelve patients in whom no recurrence had taken place within several months of healing. Its use apparently adds another substance to the list of chemical agents for the local

destruction of cancer. It may be used either by surface application or by intratumoral injection. Great care and judgment must be exercised in the latter method, because of a possible great destruction of vital parts.

GIANT NEURONAEVUS OF THE HAIRY SCALP. P. MASSON, Ann. Surg. **93**:218 (Jan.) 1931.

This article contains an interesting histopathologic analysis of an unusual giant nevus of the scalp in a child of 3 years. Clinically, the lesion was classified with the pachydermias of the hairy scalp as described by Jadassohn.

THE EXPERIMENTAL USE OF A LARGE QUANTITY OF RADIUM IN TREATMENT. W. S. LAZARUS-BARLOW, Ann. Surg. **93**:371 (Jan.) 1931.

An interesting analysis of the treatment in 108 cases of advanced malignant conditions by the equivalent of 2.5 Gm. of radium element is presented.

WIEDER, Milwaukee.

ERYTHEMA INFECTIOSUM. A. L. LAWTON and R. E. SMITH, Arch. Int. Med. **47**: 28 (Jan.)) 1931.

An epidemic of this disease in Branford, Conn., is reported by the writers. These cases, ninety-seven in all, presented the clinical symptoms of an exanthematous disease which has not yet been classified.

In most of the cases the rash was the first symptom observed, appearing first on the face and consisting of rose-red maculopapules which either became confluent, remained discrete or produced a gyrate pattern. The nose and the circumoral region were generally exempt. The rash on the face lasted up to three or four days.

In from twenty-four to forty-eight hours after the onset, the eruption appeared on the arms, forearms and dorsa of the hands. The legs were involved in the same manner as the arms, the rash spreading to new areas as the older areas cleared. The trunk was involved also in some of the cases, and in some a lacelike pattern was produced by the coalescence of lesions.

The temperature ranged from normal to approximately 100 F. in the average case.

No leukocytosis was found. Inoculations of animals from nasopharyngeal washings were negative.

This epidemic was similar to other reported epidemics. Nothing was found to explain the etiology.

JAMIESON, Detroit.

MERCURIALISM FROM THE EXTERNAL USE OF MERCUROCHROME-220 SOLUBLE. D. E. H. CLEVELAND, Canad. M. A. J. **24**:272 (Feb.) 1931.

A case is reported in which 4 per cent mercurochrome-220 soluble was applied to lesions of impetigo contagiosa in a new-born infant. Ultraviolet rays were also applied. This procedure was followed for twelve days. On the seventh day, the infant had a sore mouth, salivation, albumin in the urine and a generalized erythema. The author thinks that the erythema was not due to the ultraviolet rays.

RATTNER, Chicago.

THE VARIABILITY OF SKIN REACTIONS IN ALLERGY. H. L. ALEXANDER and F. S. MCCONNELL, J. Allergy **2**:23 (Nov.) 1930.

Positive reactions of the skin in patients with hypersensitiveness are the rule in hay-fever and infantile eczema, but are infrequent in urticaria. They are more common during the first two decades than later in life. In hypersensitive patients with a positive cutaneous reaction, the response varies in intensity at different sites on the skin. In normal persons there is a similar variation in response to injections

of histamine made at different sites. This normal variation and that which occurs in clinical allergy may be due to certain influences, residing in the cells of the skin, which may modify the formation of local edema.

CASE REPORT ILLUSTRATING THE NONSPECIFIC INDUCTION OF LOCAL AND GENERAL REACTIONS IN A HAY FEVER (SYPHILITIC) PATIENT BY THE INTRAVENOUS INJECTION OF NEOSOL. A. H. W. CAULFEILD, J. Allergy **2**:60 (Nov.) 1930.

A woman, aged 36, with nerve deafness and a strongly positive Wassermann reaction had been receiving preventive injections of pollen solutions for hay-fever, the injections being given subcutaneously in the upper arms.

Shortly after the first injection of a solution of arsphenamine was begun, there developed flushing and perspiration of the face, and many wheals limited to the areas in which the pollen solutions had been injected. She also experienced ringing in the ears and a sense of fulness in the head. The general symptoms subsided quickly, but the wheals spread and coalesced, with excessive swelling of the arms which subsided slowly.

The second injection, given eleven days later, was followed by the same general and local phenomena, which, however, were greatly relieved by the injection of epinephrine.

CARO, Chicago.

LYMPHOMA MALIGNUM (HODGKIN'S DISEASE) AND LYMPHOSARCOMA. ISAAC LEVIN, J. A. M. A. **96**:421 (Feb. 7) 1931.

On the basis of his experience in more than 500 cases of lymphoma malignum and lymphosarcoma, Levin is convinced that these two diseases are nearly identical in their clinical manifestations, that they both represent a special type of malignancy and that the peculiarities in the structure and clinical manifestations of Hodgkin's disease, as compared with other types of malignancy, depend on the special character of the structure and function of the lymphoid tissue. The two diseases are phases of the same pathologic entity and they may exist in the same patient or even in the same region.

Inflammatory lymphadenitis may be a precursor of either condition; nearly 50 per cent of the cases studied involved only one side of the cervical lymph nodes in the early stages, and they all subsequently became generalized. Thus in any stage, all the lymphoid tissue must be considered as potentially malignant and must be treated accordingly. With early recognition and treatment, the prognosis should improve greatly and the life of the patient should be prolonged considerably.

THE INTRINSIC CARBOHYDRATE METABOLISM OF THE SKIN. DONALD M. PILLSBURY, J. A. M. A. **96**:426 (Feb. 7) 1931.

Experiments with rabbits' skin reveal that lactic acid, an important product of carbohydrate metabolism, is normally present in the skin. Lactic acid formation in vitro is consistently found in normal skin, except when the skin has been frozen. Decreased oxygen tension has no significant effect on in vitro lactic acid formation by the skin. In the presence of dextrose in the incubating medium, especially in phosphate buffer solution, lactic acid formation is increased. The skin of animals in which dextrose has been injected forms lactic acid in vitro in increased amounts. The lactic acid level of the skin tends to be low in starved animals and higher in well fed animals. The author concludes that a specific carbohydrate metabolism of the skin may be observed experimentally.

COLD URTICARIA AND HISTAMINE ALLERGY. L. MINOR BLACKFORD, J. A. M. A. **96**:525 (Feb. 14) 1931.

A case is reported in which urticarial wheals appeared following prolonged exposure to cold water, and in which the response of the blood pressure to an injection of histamine was greater than in the control case. Reference is made to

the work of Thomas Lewis and his co-workers, who found an unusually high histamine content of the normal skin in cases of this sort, and thus attributed these reactions to histamine or a substance like histamine.

THE TROPICAL RAT MITE, LIPONYSSUS BACOTI. BEDFORD SHELMIRE and WALTER E. DOVE, J. A. M. A. **96**:579 (Feb. 21) 1931.

Attention is called to the rat mite, *Liponyssus bacoti,* as a cause of dermatitis. About 200 cases have occurred in the region of Dallas, Texas, during the past three years. The primary lesion is an urticarial wheal or papule varying in size from that of a pinhead to that of a split pea. The lesions lack the central hemorrhagic puncta usually caused by blood-sucking organisms. Vesicles are often present in children. In many respects, the condition resembles scabies, pediculosis corporis and bites from other insects, and in children varicella must be excluded. The mites can easily be recovered from the premises of the home or about the place of work, and occasionally from the victim's body. Characteristics of the mite and means of identification are described. The authors point out also that the advent and coincidental occurrence of endemic typhus and the rat mite in northern and eastern Texas suggest that these parasites may be vectors of the disease.

RATTNER, Chicago.

SPECIFIC POLYSACCHARIDES FROM FUNGI. H. D. KESTEN, D. H. COOK, E. MOTT and J. W. JOBLING, J. Exper. Med. **52**:813 (Dec.) 1930.

A fraction that appeared to be essentially a polysaccharide was prepared from each of five yeastlike fungi and a tricophyton. Only partial specificity was found by direct precipitation against corresponding antiserums.

STUDIES ON TUBERCULOSIS (IN FOUR CHAPTERS). F. R. SABIN, C. A. DOAN and C. E. FORKNER, J. Exper. Med. (supp. no. 3) p. 1, Dec., 1930.

The first chapter of this supplement deals with the reaction of the connective tissue of the normal rabbit to lipoids from the tubercle bacillus, strain H-37.

A leukocytic invasion was found to follow the introduction of any foreign substance into the tissues, this reaction occurring after the injection of living or dead tubercle bacilli and all fractions and split products. Formation of abscesses occurred rarely during the experiments.

Succeeding injections of certain fractions soon ceased to arouse fresh emigration of leukocytes from the vessels, but injections of polysaccharide continued to stimulate leukocytosis. The polysaccharides, however, cause a very limited formation of new connective tissue, while phosphatides stimulate the formation of new tissue but elicit little response from the leukocytes.

This work has shown that the presence of the tubercle and its essential unit, the epithelioid cell, is due to lipoids from the bacillus and specificially to hitherto unknown fatty acids of high molecular weight. It does not, however, demonstrate that tuberculolipoids are the sole agents in the production of epithelioid cells and epithelioid giant cells.

These fatty acids are present in the four major partitions of the lipoids, the most potent being that derived from the phosphatide.

A marked growth of nonspecific connective tissue cells is also noted as a result of the specific reaction of the lipoids.

In chapter 3, relating to the derivation of giant cells of tuberculosis, the authors state that there are two types discriminated by the method of formation of giant cells. One type is derived from a single monocyte or epithelioid cell; the other type is formed by the fusion of cells.

The epithelioid giant cell tends to be small, simple and relatively uniform in character, formed by amitotic nuclear division. The epithelioid giant cells show extreme variation in structure and size and lack uniformity of pattern. They are formed

by a great variety of stimuli, while it is probable that only certain specific portions of the tuberculous lipoids induce the mononucleated and the multinucleated epithelioid cells.

THE GERMICIDAL ACTION OF α-MERCAPTO AND α-DISULPHO SOAPS. A. H. EGGERTH, J. Exper. Med. **53**:27 (Jan.) 1931.

Certain soaps showed a strong germicidal activity which was markedly selective according to the organisms used and the number of atoms of carbon contained in the soaps.

IMMUNIZATION AGAINST VACCINIA BY NON-INFECTIVE MIXTURES OF VIRUS AND IMMUNE SERUM. C. P. RHOADS, J. Exper. Med. **53**:185 (Feb.) 1931.

Immunity in rabbits may be induced by instilling into the nasal cavities a combined mixture of vaccine virus and specific immune serum. The proportions of this mixture are such that on intradermal inoculation no lesion is produced.

Subcutaneous inoculation also produces immunity, but a generalized vaccinia results if the mixtures are not completely neutralized. JAMIESON, Detroit.

A CASE OF DEFORMITY DUE TO YAWS. WILLARD S. SARGENT, Mil. Surgeon **68**:179 (Feb.) 1931.

In a man, aged 60, the legs were contracted and partially fixed with atrophy of the muscles and bones. The Kahn reaction was 2+ and the history of the case together with scars in the skin led to a diagnosis of deformity due to involvement of the nervous system by yaws. A photograph illustrates the deformity well.

RATTNER, Chicago.

CONGENITAL SYPHILIS: ITS MANIFESTATIONS AND TREATMENT. EARL D. OSBORNE and EDWARD D. PUTNAM, New York State J. Med. **31**:18 (Jan. 1) 1931.

A brief but concise description is presented of the chief manifestations of congenital syphilis and of their frequency and importance in diagnosis, as determined from a survey of the cases of 300 patients seen and treated in Buffalo. The authors outline some general principles to be followed in the management of familial syphilis.

The attitude of the authors regarding the treatment of the child was pessimistic prior to 1925, but since then, due to the adoption of a new scheme of therapy, their point of view has changed to one of restrained optimism as regards the curability of the disease. Their method of therapy is based on the following factors: (1) early diagnosis and the prompt institution of treatment; (2) adequacy of treatment with effective drugs; (3) persistent therapeutic effort in spite of serology; (4) short rest intervals; (5) routine examination of the spinal fluid; (6) serologic and clinical check-ups over a long period of years.

The authors have found sulpharsphenamine to be the most efficient drug and that bismuth has supplanted mercury. Both drugs are used simultaneously, and the courses are given over a period of from three to five years. Iodides are seldom of value in congenital syphilis.

DERMATOLOGY IN RELATION TO METABOLIC DISTURBANCES. WALTER JAMES HIGHMAN, New York State J. Med. **31**:65 (Jan. 15) 1931.

The author gives his conception of a modern dermatologist as an internist who understands diseases of the skin. He classifies diseases of the skin into three groups: (1) those definitely related to internal or metabolic disturbances; (2) a larger group not demonstrably so related, but in which there is a strong presumption that such a relation exists, and (3) a still larger group in which the eruption is referable mainly to outside factors which, however, cannot

operate without that modicum of general derangement inherent in the concept of susceptibility. The second and third groups overlap. He stresses the fact that, because of the varied reactions set up by a single reagent, eruptions due to drugs throw some real light on the cutaneous response to metabolic disturbances. It is the duty of the expert basing his clinical conceptions of dermatoses on the classification of Hebra and his followers to be able to appraise the dermatoses in terms of modern medicine and to know which are essentially to be regarded from the internist's point of view and which are not. TRAUB, New York.

A CASE OF THALLIUM POISONING. J. LANSBURY, Proc. Staff Meet. Mayo Clin. **5**:323 (Nov. 12) 1930.

A case is reported in which toxicity followed the use of a depilatory cream on the chin. Two weeks after applying the cream, the patient, a woman, aged 38, suffered from pain in the chest followed by a sense of constriction. The pain then shifted to the outer aspects of the lower extremities. The parts became tender, and the skin of the legs was hot, dry and shiny. She had no fever. During the third week, she suffered from hypogastric cramps, with nausea, vomiting and constipation. At this time she was found to have a faint maculopapular rash with a few purpuric spots, and the skin of the lower extremities was warm and scaly. The hair on the scalp was loose and easily pulled out. This led to an examination of the cream, which was found to contain thallium. The eyebrows and eyelashes were not involved. The scalp became completely bald, except for a fringe around the border at the level of the ears. Hypnotics were used in treating the patient, and she recovered. It was thought that the hot dry skin of the extremities and the thoracic and abdominal pains indicated involvement of the sympathetic nervous system. The name of the depilatory cream was not furnished.

EDITOR'S NOTE.—The name of the cream is "Koremlu" (*J. A. M. A.* **96**:629 [Feb. 21] 1931).

CARO, Chicago.

A NOTE ON THE TREATMENT OF ERYSIPELAS BY X-RAYS. R. HILLHOUSE JAMIESON and F. HERNAMAN JOHNSON, Brit. M. J. **1**:57 (Jan. 10) 1931.

Three cases of facial erysipelas are reported. In one case, x-rays were not used. The infection ran a protracted course in which the temperature dropped by lysis. In the other two cases, x-rays were used and the temperature dropped by crisis within twelve hours. Small doses were given daily until the patient was cured. Even the hair and eyes can be exposed, for the doses are very small, not even approaching epilating doses.

ZOSTER, VARICELLA AND ENCEPHALITIS. W. R. BRAIN, Brit. M. J. **1**:81 (Jan. 17) 1931.

Zoster (the herpes is omitted) is considered from many angles: its clinical aspects, its relationship to varicella, its epidemiology, bacteriology and complement-fixation tests. Under clinical aspects are described ophthalmic and geniculate zoster, idiopathic and symptomatic zoster, lesions of the lower motor neurons in zoster, zoster arthritis, meningitis and encephalitis. It is pointed out that almost all the patients suffering from varicella following zoster are children, and that the group in which zoster followed varicella is composed of adults. This would indicate that adults are relatively immune to the varicella virus, that immunity wanes as life goes on, and that the adult who becomes susceptible develops zoster rather than varicella.

Varicellar encephalitis is also considered fully and is compared with and differentiated from the varicella of other specific fevers. The article is rather brief, but it is interesting. It does not lend itself well to abstracting.

THE ENIGMA OF THE CHILBLAIN. RUPERT HALLAM, Brit. M. J. **1**:215 (Feb. 7) 1931.

An analysis of 100 consecutive cases showed that perniosis was essentially an affliction of youth, appearing especially in those with lowered resistance due to tuberculosis or other toxemias, in those with heart disease, or in those with hereditary weakness of the blood vessels. Histologic examination in the early stages shows a degeneration of the small vessels, accompanied by perivascular infiltration. There is no transudation of serum, as some writers claim. Some unknown factor produces the change in the walls of the smaller cuticular vessels, while another causes slowing of the blood stream. This change in the vessels is necessary before exposure to cold will cause damage to the tissues. Studies indicate that the theory of calcium deficiency in the causation of chilblain is without ground and that there is no basis for a theory of vitamin deficiency. In short, the direct etiology of chilblain is unknown and the pathogenesis is complex and still imperfectly understood.

RATTNER, Chicago.

ANIMAL PARASITES OF THE SKIN AND ITS ADNEXA. E. C. FAUST, J. Trop. Med. **34**:1 (Jan. 5) 1931.

This is an address giving the classification of the animal parasites of the skin and a few words on the symptomatology. Among the species mentioned are the protozoa and one-cell organisms; the flatworms; roundworms; ticks, mites and related forms; insects; vertebrates and invertebrates capable of producing lesions of the skin by bites, stings or contact.

ON THE OCCURRENCE OF PROTOZOAN BODIES IN THE BLOOD OF TWO PATIENTS SUFFERING FROM AN ERUPTIVE FEVER. A. J. NORONHA, J. Trop. Med. **34**:17 (Jan. 15) 1931.

The disease begins with malaise and fever for two or three days before the eruption appears. The lesions were first noticed on the trunk, spreading rapidly to the limbs, hands and feet and lastly the face. They were at first discrete, circular, slightly elevated and disappeared on pressure. They measured from 0.25 to 0.5 cm. in diameter, consisted of a central papule with an inflammatory areola and tended to coalesce as the disease progressed. No desquamation followed involution of the lesions.

In blood smears made from two cases, protozoal bodies were found with sporulation taking place. No attempt at identification has been made.

JAMIESON, Detroit.

HYPERTHYROIDISM AND PLUMAGE: NEW STUDIES OF COMPARATIVE AND EXPERIMENTAL PATHOLOGY. P. SAINTON and H. SIMONNET, Ann. de dermat. et syph. **1**:1257 (Dec.) 1930.

These studies deal with further experimental work done by the authors on the influence on the plumage of fowls and the coats of rabbits of thyroid extracts.

The authors now find that the effects obtained are specific for the thyroid and cannot be produced by extracts from other endocrine glands. Also, the alterations of the plumage can be obtained by dosages insufficient to cause toxic effects, though the changes are slower in appearance than with more intensive administration.

It was found that extracts from normal human thyroids produced the same effects as extracts from animals. In studying the results from feeding thyroid extracts obtained from simple goiter and from exophthalmic goiter, it was found that practically no effect was obtained by the former on the plumage, while the latter produced the same changes as did extracts from normal human thyroids. The iodine content of these extracts was approximately the same. These results speak in favor of the doctrine of hyperthyroidism as a basis for the exophthalmic syndrome and against the theory of dysthyroidism.

The authors found that suprarenal extract increased the action of thyroid extract on the plumage and fur, but that hemato-ethyroidin inhibited the effect of the thyroid.

From a clinical standpoint, in a study of 186 cases of hyperthyroidism the authors found 80 cases showing changes in the pilous system analogous to those observed in the experimental animals.

Is the Achromia Which Occurs in Pityriasis Versicolor Due to a Biologic Action of the Parasite? E. W. Kistiakowsky, Ann. de dermat. et syph. **1**:1264 (Dec.) 1930.

Gougerot, Blum and others have recently described cases of pityriasis versicolor showing depigmentation. The depigmentation was attributed to a biologic action of the parasite. Kistiakowsky takes direct issue with this statement and asserts that the achromia is a consequence of the protection of the infected patch from light through the presence of the parasite and the scaling which it provokes. His studies show that ultraviolet light kills the parasite and that the depigmented patch which remains is only white by contrast with the surrounding tanned skin. Thus the various designations for this depigmented type of pityriasis versicolor (achromia parasitaria, white pityriasis versicolor, etc.) are incorrect since they connote a biologically pathogenic rôle to the fungus when its contribution is merely physical.

The Bacteriology of Impetigo Bullosa and Impetigo Neonatorum. P. Balog, Ann. de dermat. et syph. **1**:1277 (Dec.) 1930.

In Egypt, these disorders are very frequent. The author in investigating their bacteriology always found staphylococci. He noted, usually enclosed in leukocytes, a diplococcus which at first seemed to be a new organism. Cultivation, however, showed it to be a form of mutation of the staphylococcus.

Comments on the Article of Dr. Balog. N. D. L. R., Ann. de dermat. et syph. **1**:1282 (Dec.) 1930.

This short note, signed only by initials, expresses the opinion that the staphylococcus found by Balog was a contaminant. By using special culture methods (pipet method of Sabouraud), it has been repeatedly demonstrated in France that all forms of impetigo are due to streptococci. The staphylococcus is a secondary invader coming from the follicular ostia, several of which, of course, are involved in the bullous lesion.

Papillomatose Papuleuse et Confluente Involving Previously Undescribed Areas. Gougerot, O. Eliascheff and M. Goy, Bull. Soc. franç. de dermat. et syph. **37**:1279 (Dec.) 1930.

Cases of this condition (originally reported as an entity by Gougerot) have shown the intermammary and epigastric regions as sites of predilection. The case recorded by Gougerot, Eliascheff and Goy, however, presented lesions only on the shoulders and neck and near the umbilicus. The eruption was otherwise typical; the distribution seemed to be due to slight pressure and rubbing of the clothes.

Darier's Disease with Bullae. Milian and L. Périn, Bull. Soc. franç. de dermat. et syph. **37**:1280 (Dec.) 1930.

Milian and Périn describe a case of this disease which presented certain atypical features serving to enlarge the clinical picture that may be exhibited in the disorder. Besides the typical lesions (verification of the diagnosis through biopsy), it was noted that the disease began about the twentieth year; there

were verrucose elements on the hands, raised placards on the palate, and bullae with clear or purulent contents. The latter were not due to a superadded infection, but constituted one of the modes of debut of the disease.

ERYTHÈME CENTRIFUGE AND DUHRING'S DISEASE. MILIAN and LEREBOULLET, Bull. Soc. franç. de dermat. et syph. **37**:1294 (Dec.) 1930.

The patient whose case is reported had annular lesions of the typical aspect and course of erythème centrifuge for six years. Then bullae developed. The authors believe that some cases of erythème annulaire are incipient or "fruste" forms of Duhring's disease, the present case being an example.

INOCULATION OF THE GUINEA-PIG WITH CHANCROIDAL MATERIAL. P. RAVAUT, RABEAU and D. HESSE, Bull. Soc. franç. de dermat. et syph. **37**:1310 (Dec.) 1930.

By intradermal inoculations, lesions ranging from papules to ulcers were obtained. From these lesions, from the third to the eighth day, a few organisms having the characteristics of Ducrey's bacillus were obtained.

Intraperitoneal inoculations were unsuccessful. By intracerebral inoculation, one doubtful success was noted. Inoculations into lymphatic glands were followed by swelling of the glands, and Ducrey's bacillus was demonstrated in the tissue.

In seems evident from these studies that the guinea-pig is more susceptible to inoculation with Ducrey's bacillus than was formerly believed.

EPINEPHRINE TEST IN MYCOSIS FUNGOIDES. J. LEREBOULLET, Bull. Soc. franç. de dermat. et syph. **37**:1313 (Dec.) 1930.

In mycosis fungoides, the author found that a subcutaneous injection of 0.001 cc. of epinephrine was followed by hypereosinophilia. The blood was counted every five minutes after the injection for thirty minutes, then at longer intervals. In the two cases tested there was also a transitory leukocytosis. The author believes that this test may have diagnostic value in atypical or incipient cases.

ALLERGIC DERMATITIS OF THE NECK FROM CONTACT WITH A DYED SCARF: RECURRENCE OF DERMATITIS AND EXPERIMENTAL LESIONS FOLLOWING EXCESS. A. SÉZARY, P. LEFÈVRE and RIVOIRE, Bull. Soc. franç. de dermat. et syph. **37**:1316 (Dec.) 1930.

In this case eczema of the neck developed a few days after the wearing of a colored scarf. Patch tests with the colored material gave positive reactions; so did the dye itself. A few days after the scarf was discarded the eruption disappeared. About one month later, the patient feasted and drank excessively during a holiday. Immediately the eruption reappeared, confined to the same location.

The authors discuss the implications involved in the recurrence. It would seem, from this experience, that a previously sensitized area may be awakened into activity by excessive alimentation. In the authors' experience this sequence of events has been encountered clinically. It indicates that an eczematous eruption of purely external origin may be influenced by diet. The proper diet in such cases is a matter of individualization.

RECURRENCE OF GRANULOMA ANNULARE AFTER ITS DISAPPEARANCE FOLLOWING BIOPSY. L. M. PAUTRIER and P. LANZENBERG, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **37**:1213 (Dec.) 1930.

A partial biopsy of the single lesion was followed by its disappearance, but a year later there was a recurrence in situ.

CURE IN A CASE OF SPOON-NAILS BY PLURIGLANDULAR THERAPY. G. MAIRE and F. WORINGER, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **37**:1214 (Dec.) 1930.

In a typical case of spoon-nails, associated with acrocyanosis and hyperhidrosis, mixed glandular therapy resulted in cure.

AN APPARENT CASE OF PORADENITIS WITH AN ACUTE COURSE AND SUPPURATION. L. M. PAUTRIER, R. GLASSER and P. LANZENBERG, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **37**:1224 (Dec.) 1930.

The patient presented voluminous bilateral inguinal adenopathy showing the clinical features of poradenitis. However, suppuration developed, not as in poradenitis in small areas, but with total involvement of the glands. Bacteriologic and other studies gave negative results for chancroid and poradenitis. The authors came to no definite opinion about the nosologic position of this case; they are inclined to think that there are cases of inguinal adenitis that are obscure and not yet classifiable.

MAST CELLS IN THE BULLA OF DUHRING'S DISEASE. A. DISS, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **37**:1238 (Dec.) 1930.

In two cases, Diss found mast cells in the serous contents. This is a rare observation having been recorded only once before by Nicolas, Rousset and Froment. In the cases of Diss, the blood showed 3 and 1.5 per cent of mast cells, respectively.

SENSITIZATION TO WHITE OF EGGS IN INFANTILE ECZEMA. P. WORINGER, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **37**:1242 (Dec.) 1930.

In breast-fed infants with eczema, Woringer found that four of thirteen were sensitive to egg white. Intradermal tests were used. The positive reactions were urticarial, never eczematous. Passive transfer tests for egg white were positive in three of the four cases; in the other case there was a positive Prausnitz-Kustner test to fish. There was unquestionably a specific allergy in these cases, but the author does not believe that the eczema was due to sensitivity to egg white. His patients had received no egg and the application of egg to the skin never produced an eczematous response. Suppression of the incriminated food has been ineffectual in Woringer's experience. He thinks that in eczema of infants there is always an allergy to alimentary proteins but that this allergy is only a sign of the special state of the skin. "In other words, allergy is the terrain upon which eczema appears, but eczema is not allergic, in the true sense of the word; as is urticaria, for example. It is, one might say, a para-allergic affection."

VERNES-RESORCIN REACTION IN SOME CASES OF CUTANEOUS TUBERCULOSIS. A. ULLMO, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg) **37**:1245 (Dec.) 1930.

Of thirty-nine cases of lupus vulgaris, six gave a reaction above thirty; of ten cases of lupus erythematous, three gave a reaction above thirty; one case of gummose tuberculosis showed a reaction at forty-two; of four cases of tuberculosis verrucosa cutis, one gave a reaction at thirty; and four cases of tuberculids showed all reaction below thirty. Moreover, there was no relation between the intensity of the disease and the reaction, since some of the most severe cases gave negative reactions. The results therefore are distinctly discordant.

MICHAEL, Houston, Texas.

CHLORORACHIA. E. VAMPRÉ and O. LANGE, Arch. brasil. de med. **20**:279 (July) 1930.

The normal amount of chlorides in the spinal fluid varies between 7 and 7.40 Gm. per thousand cubic centimeters. Hyperchlororachia has been found in cases of nephritis with retention of chlorides in the plasm, and in cases of neurosyphilis. Hyperchlororachia has a good prognosis in cerebrospinal syphilis, and hypochlororachia a poor prognosis in cases of severe neurosyphilis. In acute infectious meningitis, there is always a lower chloride content of the spinal fluid. A chloride content of less than 6 Gm. per thousand cubic centimeters should point to tuberculous meningitis.

SYPHILITIC CHOREA. WALDEMIRO PIRES, Arch. brasil. de med. **20**:431 (Nov.) 1930.

In ten cases of chorea the author noted a history of congenital syphilis and syphilitic stigmas; treatment with bismuth and arsphenamine resulted in recovery. In fifty cases there were no signs or history of syphilis, and serologic reactions were negative. Specific treatment with bismuth and arsphenamine failed to produce improvement.

PARDO-CASTELLO, Havana, Cuba.

CUTANEOUS ALLERGY IN VENEREAL DISEASE: COMPARISON, INTERPRETATION AND DIAGNOSTIC VALUE. EDUARDO DE GREGORIO and GARCIA-SERRANO, Ecos españ. de dermat. y sifil., November, 1930, p. 67.

Cutaneous reactions with the streptobacillus vaccine (Ducrey) of Nicolle and Durand (Dmelcos) in chancroid, gonorrhea, syphilis, psoriasis and acute inguinal lymphogranulomatosis were studied. Positive reactions in from 94 to 99 per cent of cases of Ducrey's infection have been reported in the literature. The authors' statistics confirm these results.

In a group of patients who were free from soft chancre and who gave a negative history for this infection, uniformly negative results were obtained. The author considers this an important, accurate and specific diagnostic test in chancroid.

The method of performing the test is described in detail, and a complete exposition of the method of interpreting the results is also given.

MENINGEAL HERXHEIMER REACTION. CARO-PATON, Ecos españ. de dermat. y sifil., November, 1930, p. 99.

A case is reported in which intolerance to arsenic was manifested by symptoms in the central nervous system.

A housewife, aged 32, who had been married for ten years and who had six healthy living children, with no miscarriages, presented herself for examination because of a pruriginous eruption, the history and clinical appearance of which suggested urticaria. The husband admitted having had a primary lesion before marriage and he had been receiving antisyphilitic treatment.

The Wassermann reaction was frankly positive, and an initial dose of 0.15 Gm. of neoarsphenamine was administered, to which the patient reacted with a slight headache. Seven days later another injection of 0.3 Gm. of neoarsphenamine was given, and the patient reacted with intense fever, vomiting and headache. Five days later she had a generalized pruriginous erythema, complete right facial paralysis, ringing in the ears and deafness, particularly on the right side.

After she had received iodides and bismuth, it was thought best to give 0.15 Gm. of neoarsphenamine. The meningeal symptoms returned. After improvement from the last reaction, arsenic (acetyl arsenic) in another form was given intramuscularly, and the patient again reacted as in the first instance.

A Case of Psoriasis and Scabies. Pedro L. Baliña, Elias Gavina Alvarado and Guillermo Basombrio, Rev. argent. de dermat.-sifil. **13**:2 (Dec.) 1930.

The authors report the case of a man, aged 30, a bathkeeper, who had had psoriasis for nine years. For the past two months skin lesions characteristic of scabies, and accompanied by intense nocturnal itching had developed. Questioning revealed the fact that some other members in the same household were also afflicted with scabies. This combination is considered rare.

A Case of Erythromelia of Pick. Pedro L. Baliña and Milio Fernandez Blanco, Rev. argent. de dermat.-sifil. **13**:14 (Dec.) 1930.

The authors reported a case of erythromelia (Pick) which had been under observation for five years. Their patient was a chauffeur, aged 39, in whom the disease had been present for two years. The condition began as red spots that appeared on the backs of the hands, and later became violaceous and persisted. This gradually spread to the four extremities. The skin of the affected portion was violaceous. In some parts it was slate color. The skin became thinned, atrophied, roughened, etc., with a diminution in the function of perspiration. The portions affected were the hands, wrists, forearms, elbows, arms, feet and legs, and there was slight erythema of the thorax and the abdomen.

The histologic examination gave results typical of erythromelia (Pick). The laboratory and physical examinations gave essentially negative results.

A discussion of the differential diagnosis, a review of the literature and a number of photographs to illustrate the clinical and histologic features of the disease were all well presented. During the five years that the case was under observation, the etiology was not found. The disease gradually progressed with some remissions and exacerbations. Eczema developed in some of the affected portions. The treatment did not affect the course of the disease. A complete cure has never been reported. This case was not accompanied with syphilis.

Chancre and Parapsoriasiform Syphilid Occurring in a Case of Common Hereditary Psoriasis. Pedro L. Baliña, Rev. argent. de dermat.-sifil. **13**:46 (Dec.) 1930.

The case reported occurred in a young man, aged 21, who presented typical lesions of psoriasis. Following exposure, an initial lesion developed on the anterior surface of the upper third of the thigh followed by adenopathy on the same side. Fever, malaise, etc., ushered in the secondary eruption which had the typical picture of parapsoriasis.

Three photographs accompany the article demonstrating in the same patient at the same time chancre, inguinal adenopathy, parapsoriasiform syphilid and psoriasis. Specimens for biopsy were refused, which made microscopic study of the case impossible.

Juxta-Articular Nodes. Pedro L. Baliña, G. Basombrio and E. A. Aubrun, Rev. argent. de dermat.-sifil. **13**:54 (Dec.) 1930.

The literature on this subject is reviewed. The symptomatology, etiology and the pathologic histology of the disease is discussed as a preface to the report of two cases presented by the authors.

The two cases reported occurred in men with no history of syphilitic infection, but in whom the Wassermann reaction of the blood was 4 plus. In one of the cases leukoplakia of the mouth was evident, and the biopsy from this patient suggested a tuberculous structure, but other features led the pathologist to believe that he was dealing with a syphilitic process.

The authors believe that in their two cases the etiology of the disease was syphilis. They base their conclusion on the following observations: (1) the presence of syphilitic cutaneous lesions in both patients; (2) the strongly positive

Wassermann reaction in both patients; (3) the disappearance of the lesions under antisyphilitic treatment, and (4) the histologic observations suggestive of syphilis.

CIPOLLARO, New York.

KERATOSIS FOLLICULARIS AND SPINULOSA (LICHEN SPINULOSUS) FOLLOWING THE ADMINISTRATION OF ARSPHENAMINE OR ARSENIC. C. BRUHNS, Dermat. Wchnschr. **91**:1844 (Dec. 20) 1930.

Bruhns reports three cases in which follicular keratosis developed following treatment with arsenicals. In the first it appeared after a generalized arsphenamine dermatitis, in the second during the course of arsenic treatment for lichen planus, and in the third during a course of neoarsphenamine for latent syphilis without a preceding dermatitis. Clinically the lesions presented the grater-like sensation on rubbing that is found in lichen spinulosus, but the long horny prickles were not present. The literature is reviewed and the author concludes that this is one of the more unusual manifestations of hypersensitivity to arsenic.

AN EXANTHEMATOUS APPEARING ENDOTHELIOMA CUTIS. HANS KÖNIGSTEIN, Dermat. Wchnschr. **91**:1851 (Dec. 20) 1930.

The author describes a patient observed over a period of five years in whom groups of papules developed and faded in crops on the face, trunk, inner surfaces of the thighs and on the labia. Histologically these lesions were endotheliomas.

THE EMPLOYMENT OF ACETARSONE IN PEMPHIGUS VULGARIS CHRONICUS AND VEGETANS WITH OBSERVATIONS ON ACETARSONE THERAPY. M. OPPENHEIM, Dermat. Wchnschr. **91**:1855 (Dec. 20) 1930.

Oppenheim has had a number of good results from the use of a brand of acetarsone, N. N. R., in the treatment of conditions belonging to the pemphigus group. He advises that it be tried in these cases and points out that a satisfactory result is more likely if treatment is started in the early stages. The dosage should be adequate and must be continued over a considerable period.

THE BIOLOGY OF PAPILLOMA OF THE SKIN AND OF THE MUCOUS MEMBRANE. E. V. ULLMANN, Dermat. Wchnschr. **91**:1864 (Dec. 20) 1930.

Ordinary flat warts and extensive laryngeal papillomas have the same etiology, namely, a filtrable virus. Filtered extracts of these papillomas produce warty lesions when injected into the skin of a suitable animal (dog) or into human skin. There is a considerable variation in virulence and in the resistance of individuals.

THE DIET THERAPY IN DISEASES OF THE SKIN. R. VOLK, Dermat. Wchnschr. **91**:1869 (Dec. 20) 1930.

Good results have been obtained by the use of the Sauerbruch-Hermannsdorfer diet in lupus vulgaris. This diet has also been used in the treatment for tuberculids, psoriasis, lichen planus, eczema, prurigo, pemphigus and other cutaneous conditions. Other methods of treatment should be carried out along with the salt-free diet. The author has seen no serious effects from the withdrawal of salt. The theoretical possibilities of the mode of action of this treatment in lupus vulgaris are discussed.

INVESTIGATIONS CONCERNING "BLACK SKINWRITING" ("SCHWARZE HAUTSCHRIFT"). EMIL HOSP, Dermat. Wchnschr. **91**:1895 (Dec. 27) 1930.

Various authors have reported that a black streak occurs on the skin in certain persons when they are stroked with metal rods. They have designated the reaction as a black dermographism and have stated that it is associated with hysteria. Hosp investigated the phenomenon in 225 patients with various condi-

tions, including five cadavers. He used small rods of pure silver, copper, aluminum, lead and zinc, and under suitable conditions he was able to elicit the reaction in every instance. He found that it was a purely mechanical action in that tiny particles of the metals were deposited on the skin if it was free from fat, and he also found that the presence of even small amounts of powder containing zinc oxide, barium sulphate, calcium sulphate, calcium carbonate, silica dioxide or various other substances materially assisted in this mechanical deposition. The sign has no reference to hysteria and is not in any sense a dermographism.

THE MORPHOLOGY OF LICHEN RUBER PLANUS ON THE SKIN OF THE FACE. M. FELLNER, Dermat. Wchnschr. **92**:1 (Jan. 3) 1931.

The author discusses the rarity of lichen planus on the face and also the fact that it is unusual in children. His patient was a boy, aged 9, who presented typical lichen planus of the upper extremities with an eruption of the face that was suggestive of pityriasis simplex and also ringed lesions on the neck which resembled dermatophytosis. Histologic examination of the latter lesions showed a characteristic process. The eruption cleared leaving the usual marked hyperpigmentation.

A SOLUTION OF THE PROBLEM OF COLORIMETRY IN DERMATOLOGY. ROMAN VON LESZCZYŃSKI, Dermat. Wchnschr. **92**:6 (Jan. 3) 1931.

The author has designed a colorimeter for the purpose of recording accurately the color of any cutaneous lesion. He uses five basic colors: white, black, blue, yellow and red. These colors can be adjusted to occupy any segment of a circle and the resulting color is observed by revolving the circle rapidly. The segments occupied by the various colors are altered until on rotating the disk the shade of the eruption is reproduced. The color is then recorded in the number of degrees of the circle occupied by each of the five colors.

THE ETIOLOGY OF INTERDIGITAL ECZEMA. H. GRASREINER, Dermat. Wchnschr. **92**:12 (Jan. 3) 1931.

A case is described in which an eczema occurring between the toes was apparently due to the wearing of brown shoes.

HEMATOMA OF THE NAILBEDS IN A CASE OF POSTENCEPHALITIC PARKINSON'S DISEASE. F. V. POÓR, Dermat. Wchnschr. **92**:45 (Jan. 10) 1931.

A patient with Parkinson's disease which followed an epidemic encephalitis presented subungual hematomas. This was the second attack in the same patient. The condition was considered to be due to a nerve influence.

ERYTHEMA ANNULARE CHRONICUM MIGRANS (LIPSCHÜTZ). Z. A. KRESTANOW, Dermat. Wchnschr. **92**:48 (Jan. 10) 1931.

Following the bite of *Ixodes ricinus* (dog tick), an area of erythema appeared and spread peripherally. The development was slow and continued to a maximum diameter of 40 cm. in the course of two months, and cleared spontaneously. There were no subjective symptoms and no resulting atrophy or pigmentation. The condition was considered to be a typical example of erythema chronicum migrans (Lipschütz). The author states that the disease differs markedly from Darier's erythema annulare centrifigum.

CRITICAL CONSIDERATION OF "DERMATITIS NODULARIS NECROTICA." FRIEDRICH FISCHL, Dermat. Wchnschr. **92**:50 (Jan. 10) 1931.

The literature concerning this disease is briefly but critically reviewed. The author considers the condition a form of papulonecrotic tuberculid and the special terminology superfluous and misleading.

THE EXTERNAL TREATMENT OF ROSACEA. JOSEF SELLEI, Dermat. Wchnschr. **92**:53 (Jan. 10) 1931.

Sellei advises electric cataphoresis as local treatment for rosacea in addition to the indicated general medical therapy. He uses a 4 per cent solution of caffeine sodium salicylate first, for from five to ten minutes with a current of 2 to 3 milliamperes, followed after a short rest by a 1:20,000 solution of epinephrine. Daily treatments for from twenty-five to thirty sittings are desirable, and the best results are obtained in the cases in which the seborrheic element is not predominant.

THE TREATMENT OF THE VARIOUS FORMS OF SYPHILITIC MESAORTITIS. G. SCHERBER, Dermat. Wchnschr. **92**:56 (Jan. 10) 1931.

The author emphasizes the importance of early treatment of syphilis as a preventive of aortitis. He outlines his course of treatment for various types of syphilitic aortitis, prescribing stimulants for the heart and rest as indicated in conjunction with specific therapy. Neoarsphenamine is given in small and increasing doses after a preliminary course of mercury and iodide. Foreign protein shock therapy in the form of boiled milk is useful at times, as is malaria therapy. In early cases, improvement of the pathologic process is to be expected, while in later cases palliation is usually possible.

A COMPARISON OF THE PRECIPITATION REACTIONS (KAHN TEST; MEINICKE TEST) WITH THE WASSERMANN REACTION IN TWO THOUSAND FIVE HUNDRED SERUMS. WERTHER and LISA BAARS, Dermat. Wchnschr. **92**:61 (Jan. 10) 1931.

The authors conclude that: 1. The Kahn and Meinicke tests are equally sensitive. 2. These tests are more sensitive than the Wassermann reaction and remain positive longer in latency and under treatment. They should be considered as complementary to the Wassermann test. 3. In four cases of primary syphilis, the precipitation reactions were positive fourteen days before the Wassermann reaction became positive. 4. The Wassermann test is advised as a control to check possible false positive reactions which are more frequent with the Kahn and Meinicke reactions.

BLASTOMYCOSIS CUTIS ULCEROSA. OSKAR KIESS, Dermat. Wchnschr. **92**:90 (Jan. 17) 1931.

A patient is described who presented a multiform, generalized eruption consisting of bullae, serpiginous ulcers, abscesses and scaly papules with, at times, a rise in temperature. Round and oval double contoured bodies were demonstrated in the pus and a pure culture of this organism was eventually obtained. The lesions cleared under therapy with iodide.

GONORRHEAL SKIN INFECTION IN A BABY. LYDIA HENNING, Dermat. Wchnschr. **92**:96 (Jan. 17) 1931.

In the course of treating a severe gonorrheal infection of the bladder, vagina and rectum of a 5 months old baby, a bullous eruption developed on the back and sides of the trunk with severe general symptoms. Gonococci were readily demonstrated in the contents of the bullae but not in blood cultures.

TAUSSIG, San Francisco.

THE OLDEST HISTORY OF THE SO-CALLED ERYTHEMA INFECTIOSUM. MILANA KAZAROWA, Dermat. Wchnschr. **92**:99 (Jan. 17) 1931.

The author points out that the first description of this disease was by Willan in his textbook, published in 1805. It was described under the name of "Rubeola (measles) sine Catarrho."

REMARKS ON BUCKY'S GRENZ RAY TREATMENT. ALBERT BÜRKMANN, Dermat. Wchnschr. **92**:102 (Jan. 17) 1931.

The "Mekapion" of Strauss is advised as a measuring instrument in giving treatments with Grenz rays in order to overcome the uncertainty of dosage that is otherwise inherent in the method. The author reports an unusual case in which 600 R caused an ulcerative reaction, though this dose is only two thirds of that which ordinarily causes a mild erythema. He suggests hypersensibility to the soft rays as an explanation for this reaction.

THE COLD CAUSTIC AS THE METHOD OF CHOICE IN THE REMOVAL OF SOFT FIBROMAS, MULTIPLE WARTS AND OTHER NEOPLASMS OF THE SKIN. RICHARD BRAUN, Dermat. Wchnschr. **92**:104 (Jan. 17) 1931.

The author advises the use of the bipolar diathermy current for the destruction of small benign tumors. He has a special handle with a current interrupter in which he uses an ordinary needle, selecting a very fine one for tiny growths and coarser ones for the larger lesions. As a rule no anesthetic is required, providing the needle is inserted before turning on the current. The indifferent electrode is held by the patient.

UNUSUAL LOCATIONS OF PRIMARY SYPHILITIC LESIONS. H. W. RILLE, Dermat. Wchnschr. **92**:109 (Jan. 17) 1931.

Six case histories are given of patients presenting chancres on the trunk. None of them was on the breast. The author emphasizes the fact that lesions on the chest and on the upper part of the back were associated with axillary adenopathy, while those of the abdomen caused enlargement of the inguinal glands.

THE TREATMENT FOR SYPHILIS OF THE BLOOD VESSELS. HANS VÖRNER, Dermat. Wchnschr. **92**:115 (Jan. 17) 1931.

Because of the beneficial results seen in seven patients with symptoms of syphilitic disease of the heart and the blood vessels, the author suggests intravenous injections of red mercuric bisulphids. The course of treatments consisted of doses of 0.1 Gm. at intervals of three or four days for four or five doses, repeated as indicated. This treatment is considered specific only for involvement of blood vessels.

A CORDLIKE ERUPTION OF THE SKIN FOLLOWING LYMPH CHANNELS IN ASSOCIATION WITH A CUTANEOUS INJURY. JULIUS HELLER, Dermat. Wchnschr. **92**:137 (Jan. 24) 1931.

Heller describes two patients in whom linear, eczema-like eruptions developed on the leg. In each instance the eruption was preceded by an injury. He discusses the possible genesis, briefly reviews similar cases that have previously been reported and concludes that irritation of the lymph channels is the causative factor.

THE DIAGNOSIS OF LICHEN PIGMENTOSUS. N. M. FRISCHMAN and W. B. BERSON, Dermat. Wchnschr. **92**:139 (Jan. 24) 1931.

A boy, aged 12 years, presented an eruption consisting of pigmented macules, varying in size from that of a millet seed to that of a lentil, scattered over the trunk and the upper portions of the thighs. At the borders of a few of the lesions, lichenoid papules were seen. There were no subjective symptoms. The differential diagnosis is discussed with special consideration of melanoderma toxica lichenoides. The authors conclude that their case is a typical example of lichen pigmentosus.

OBSERVATIONS ON THE TREATISE OF SAN.-RAT SOMOGYI: "INDUSTRIAL INJURY OF THE SKIN BY SODIUM CHLORIDE." S. VON SZENTKIRÁLYI, Dermat. Wchnschr. **92**:146 (Jan. 24) 1931.

In addition to the multiple ulcers described by Somogyi, the author has observed a number of cases presenting only a single deep ulcer due to the action of sodium chloride. Certain of these ulcers seem to be on a syphilitic basis.

AN UNUSUAL ACCIDENT FROM THE INJECTION OF A NONSPECIFIC MILK PREPARATION (AOLAN). F. ORTMANN, Dermat. Wchnschr. **92**:148 (Jan. 24) 1931.

The patient, under treatment for acne indurata, had received two intracutaneous injections of a nonspecific milk preparation and one intragluteal injection eight days before. He was given 8 cc. of the milk preparation intramuscularly, and one-half minute thereafter had a severe reaction with difficulty in breathing, cyanosis and swelling of the face. The author considers the possibility of an accidental intravenous injection, although the usual precautions were followed. He also suggests an anaphylactic type of reaction.

RESEARCHES ON THE BASIC FACTORS OF ACNE ROSACEA. DANKMAR HACHENBURG, Dermat. Wchnschr. **92**:165 (Jan. 31); 197 (Feb. 7) 1931.

Microscopic examinations of the capillaries were made in fifteen of the fifty cases studied. In general, the hairpin form of the capillary loops was not well maintained and aneurysms were frequently seen.

Most of the patients presented nervous stigmas, chiefly in the form of a fine tremor, psychic instability, dermographism and a spastic condition of the smooth musculature. Many showed marked sensitiveness to changes in temperature.

Interferometric investigations of the decomposition value for various glands of internal secretion were carried out in twenty-five patients and demonstrated a frequent disturbance in the correlation of these glands to one another.

Particular features of the physical examinations are briefly commented on. Blood pressure was considerably increased in more than half of the cases, and in none was it below 110 mm.

The author concludes that the patient with acne rosacea nearly always presents a disturbance of important body functions, often on the basis of a "vegetative neurodysergia."

A CASE OF GRANULOMA ANNULARE CURED BY BUCKY RAYS. LUDWIG BAER, Dermat. Wchnschr. **92**:171 (Jan. 31) 1931.

A woman, aged 45, with lesions of granuloma annulare on the backs of both hands was treated with oversoft roentgen rays, resulting in the complete disappearance of the lesions. Roentgen irradiation the previous year had been without effect. The patient presented signs of healed pulmonary tuberculosis and there were several instances of tuberculosis in her immediate family.

A NEW PYROGALLOL-SULPHUR-CHOLESTEROL PREPARATION FOR THE COLORING, CARE AND GROWTH OF THE HAIR. A. STRAUSS, Dermat. Wchnschr. **92**:174 (Jan. 31) 1931.

Strauss discusses the action of pyrogallol, sulphur and cholesterol on the hair and advises an alcoholic solution of thiopyrogallolcholesterol as a combined dye and hair tonic.

THE PATHOGENESIS OF DUHRING'S DERMATITIS HERPETIFORMIS. A. VARGA, Dermat. Wchnschr. **92**:193 (Feb. 7) 1931.

The history of a case of dermatitis herpetiformis, in which considerable laboratory research was carried out is given. The author concludes that the disease is due to an infection or a toxic injury, and explains the characteristic symmetrical distribution as being due to involvement of the nervous system.

EXPERIMENTAL CONGENITAL SYPHILIS IN RABBITS. J. A. FINKELSTEIN and S. S. ORLOW, Dermat. Wchnschr. **92**:203 (Feb. 7) 1931.

The offspring of syphilitic rabbits, infected by the cutaneous or intrascrotal method, showed no signs of syphilis and were readily affected by a new infection. Intravenous injection of emulsions of spirochetes into pregnant females occasionally resulted in intra-uterine infection. Repeated pairing of a healthy male with a syphilitic female sometimes resulted in infection of the male.

A SUBSTANCE IN THE SERUM OF PATIENTS WHO HAVE HAD AN ARSPHENAMINE DERMATITIS WHICH INCREASES THE REACTION OF THE SKIN OF PERSONS SENSITIVE TO ARSPHENAMINE. E. NATHAN and H. GRUNDMANN, Dermat. Ztschr. **60**:127 (Jan.) 1931.

The authors show by a series of experiments that the intracutaneous injection of active serum from a patient who has had a dermatitis caused by the injection of arsphenamine increases the size of the urticarial reaction caused by subsequent intracutaneous tests with arsphenamine. The same effect occurs if the solution of arsphenamine is mixed with the active serum of a patient who has had a dermatitis produced by arsphenamine or who has been artificially sensitized. The possible character of the substance causing this phenomenon is discussed.

LUPUS AND CARCINOMA. ASTA V. MALLINCKRODT-HAUPT, Dermat. Ztschr. **60**:138 (Jan.) 1931.

Between 1920 and 1930, 906 patients with tuberculosis of the skin were seen in the Bonn clinic. Most of them had lupus vulgaris. Of these, 28 or 3.09 per cent presented lupus carcinoma. The case histories and photographs of 7 of these are given. Previous therapy is not considered a causative factor except that early effective treatment is a preventive measure.

LICHEN PLANUS AND CISTERNAL PUNCTURE. ERICH HOFFMANN, Dermat. Ztschr. **60**:165 (Jan.) 1931.

Cisternal puncture was done on eight patients with lichen planus. The itching was markedly improved and at times the eruption decreased. The fluid was normal except that in three instances a slight variation in the colloidal gold curve was found.

STORMY PROVOCATION OF A LONG-STANDING SYMPTOM-FREE TABES AS A RESULT OF TREATMENT WITH ARSPHENAMINE. MARTIN SCHUBERT, Dermat. Ztschr. **60**:169 (Jan.) 1931.

A patient had been treated for a chancre four years previously. He presented a weakly positive Wassermann reaction with no specific symptoms and was started on antisyphilitic therapy. Following the third injection of neoarsphenamine (0.45 Gm.), a severe reaction developed immediately, which included vomiting, severe pain in the lower portion of the back radiating to the legs, and retention of urine and stools. After a few days, typical lancinating pains occurred, and a slowed pupillary reaction was observed. The differential diagnosis of myelitis hemorrhagica, pseudotabes and tabes is discussed. The conclusion is that symptomless tabes had been made manifest by the shock of a reaction to arsphenamine.

TAUSSIG, San Francisco.

DERMATOLOGIC ABSTRACTS

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

MALARIA TREATMENT OF NEUROSYPHILIS. R. C. ROBERTSON, U. S. Vet. Bur. M. Bull. **7**:25 (Jan.) 1931.

All nine cases reported by Robertson have shown a marked mental improvement following malaria therapy. Some of the patients are earning a living at former occupations, others are working at occupations of a simpler character, and all have made a fair social adjustment. In the cases in which an examination of the spinal fluid was made at the conclusion of the treatment, a distinct improvement of the condition observed before treatment was noted. The greatest improvement in cerebrospinal fluid was observed in the colloidal gold reaction and in the cell count. There seemed to be little change in globulin or in the Wassermann reaction of the spinal fluid. There was no change in the Wassermann test of the blood. The speech defect in some cases seemed to improve. There appeared to be the greatest improvement in the maniacal type of patient. It is thought that malaria therapy is justified because of its simplicity of technic, the fact that it is easily controlled, its relative harmlessness, and the fact that it produces the greatest percentage of improvement in cases of dementia paralytica.

HISTOLOGY AND PROGNOSIS OF BUCCAL CARCINOMA. R. PHILLIPS, Lancet **1**:118 (Jan. 17) 1931.

Phillips has made a study of 319 cases of buccal carcinoma from the points of view of histology and clinical course, and of 71 cases as regards response to irradiation. The accuracy and usefulness of Broders' histologic classification of epitheliomas have been demonstrated. A well marked correlation between the histology and the clinical course of buccal carcinoma has been obtained. This correlation is found especially in the postoperative length of life, the total duration of the disease and the prospects of cure. These are increased the greater the differentiation of the carcinoma and decreased the greater its anaplasia. No direct relationship was found between the histology of buccal carcinoma and its response to irradiation. A hypothesis is suggested to explain this apparent exception to the general correlation between the histogenesis and the biology of buccal carcinoma. The possible use of this hypothesis in the radiotherapy of buccal cancer is suggested as enabling the most suitable method of irradiation to be applied according to the histology of the growth.

BISMUTH OXYCHLORIDE OINTMENT IN TREATMENT OF LUPUS ERYTHEMATOSUS. R. M. B. MACKENNA, Lancet **1**:126 (Jan. 17) 1931.

A preliminary report is submitted by MacKenna on the treatment for chronic lupus erythematosus with bismuth oxychloride ointment. Of a series of nineteen cases of chronic lupus erythematosus, all of which have benefited from the use of the ointment, ten are reported in detail. Of these, five have been cured by the use of the ointment, in conjunction with injections of bismuth, and the clinical reports indicate that in many cases the disease may be cured by the local application of the ointment, without injections of bismuth. Cases have been quoted showing that the ointment appears to have a slight antiseptic or bactericidal effect; the ointment has been employed with advantage in two cases of tinea unguium and in two cases diagnosed as chancroid. It is shown that, while the ointment may be of value as a local application in the treatment for yaws and syphilis, it is valueless if administered by inunction.

VENEREAL GRANULOMA. E. HVAL, Norsk mag. f. lægevidensk. **91**:1223 (Nov.) 1930.

In Hval's patient, a sailor previously treated in several places for secondary syphilis, there was the typical picture of venereal granuloma. Microscopic examination of the granulation tissue revealed, partly in the large mononuclear cells, partly in groups outside the cells, the Donovan bodies characteristic of this disease. Infection had occurred in South America. Venereal granuloma has not before been observed in Norway.

SUBACUTE INGUINAL LYMPHOGRANULOMATOSIS. E. HVAL, Norsk mag. f. lægevidensk. **91**:1229 (Nov.) 1930.

In the four cases reported, microscopic examination of the lymph nodes disclosed a granulation tissue with abundant cells. There were numerous small, irregularly defined abscesses, often with central necrosis. The micro-abscesses were surrounded by a border of epithelioid cells with occasional cells having two or three nuclei and also occasional Langhans' giant cells. The abscesses presented a polymorphic picture. Hval says that diagnosis cannot be based on the microscopic changes alone. He considers Wilhelm Frei's intracutaneous antigen reaction of great value in the diagnosis. This reaction was positive in the four cases.

PRIMARY TUBERCULOSIS OF THE SKIN. G. GULDBERG, Norsk mag. lægevidensk. **91**:1235 (Nov.) 1930.

In Guldberg's patient, a boy aged 13, of a healthy family, there were continued granulation and suppuration in one of three wounds on the knuckles of the left hand following a trauma. A lymphadenitis developed in four or five weeks in the left forearm and two weeks later in the left axilla and gradually took on the picture of a tuberculous lymphadenitis with formation of fistula. Tubercle bacilli were demonstrated in the wound and in the abscesses of the lymph nodes. Clinical and roentgen examination of the lungs showed no signs of tuberculosis. The Pirquet test was positive three months after the occurrence of the wound. The case is considered as primary tuberculosis of the skin with regional lymphadenitis.

Society Transactions

ST. LOUIS DERMATOLOGICAL SOCIETY

MARTIN F. ENGMAN, JR., M.D., *Secretary*

Regular Meeting, May 14, 1930

RICHARD S. WEISS, M.D., *Presiding*

DERMATITIS DUE TO PHENOLPHTHALEIN. Presented by DR. JOSEPH GRINDON.

A young man, first seen about three weeks previous to presentation presented some dry, brownish patches next to the mouth and on the chin. There were also similar darker patches on the back of the neck and near the right elbow. There were a few pink patches on the left forearm that had developed more recently. When the patient was presented, these patches had faded, except those near the right elbow. The itching had ceased. The patient had been using "Feen-a-mint" occasionally for one year until three weeks previous to presentation.

DISCUSSION

DR. S. T. MILLARD, Topeka, Kan.: Did the young man say that the itching had been very intense?

DR. J. GRINDON: Yes, sometimes there was severe itching that he attributed to "hives."

NEUROTIC DERMATITIS. Presented by DR. E. E. BROWN.

A woman, aged 36, a housewife, complained of severe itching caused by the presence of bugs or larvae under the skin. She claimed that she could expel worms through or out of varicose ulcers and also from warty growths in and around the vulva. The duration was since August, 1929. The patient was treated for scabies at the Barnard Free Skin and Cancer Hospital. She was also examined at the City Hospital and at St. Mary's Infirmary.

DISCUSSION

DR. S. J. MILLARD, Topeka, Kan: I had one such case, but I could not find a cure. I had the usual experience of having the patient tell me that there were parasites, so I looked under the arms but there were none there. Several months later I met her and she seemed very well. I asked her what she had done, and she told me she had been to a physician — a general practitioner whom I knew well. On asking him what he had one, I was advised that he had told her that there was something there; that he had given her a strong sulphuric salve, which caused a dermatitis, and that he had then soothed it until the irritation as well as the itching had disappeared. The case was plainly a neurotic one.

LICHEN PLANUS. Presented by DR. ERICH BROCKELMANN.

The patient, a white man, aged 46, a clerk, said that about six years previously he had noticed whitish patches in the mouth which spread gradually. He went to several dentists who used strong local applications and treated him for pyorrhea. At this time the patient chewed tobacco and smoked a pipe excessively.

There were no subjective symptoms, except for a slight stinging sensation when he ate spicy food.

The involved area covered the entire mouth except the lingual mucous membrane and the mucosa adjacent to the lips. It consisted of grayish thickened patches of irregular shape partly connected by bridgelike bands. A subacute inflammation was associated with it.

Bacteriologic as well as microscopic examination of the secretions showed nothing characteristic.

The Wassermann reaction was negative.

DISCUSSION

DR. R. S. WEISS: I am quite sure that all of us will agree that this is a case of lichen planus of the oral mucosa. In this connection it might be interesting to mention a case that I saw recently.

A woman, about 45 years of age, consulted me a few months ago complaining of a sore tongue. She presented circumscribed, grayish-white, oval plaques about 2 by 5 cm. in size on the right side of the tongue. I considered the condition leukoplakia and after consultation with Dr. Ellis Fischel, the lesion was excised completely with the cautery knife. On microscopic examination it proved to be typical lichen planus, and the patient appeared later with lichen planus of the buccal mucosa.

In considering the diagnosis of lesions of the oral mucous membranes, it is always important to keep lichen planus in mind.

CONGENITAL JUVENILE XANTHOMATOSIS. Presented by DR. NORMAN TOBIAS.

R. P., a white girl, aged 1 year, had an eruption on the face and on the upper part of the chest and the back which was noticed a few days after birth. The lesions were discrete, slightly elevated, flat, rounded tumors of a uniform yellowish color. They were most profuse on the face. The lower lids were also involved.

No history of a hereditary condition or of jaundice was given. The lesions on the chest and back were light brown pigmented macules. Irritation by rubbing produced no change in these lesions.

Examination of the blood showed: red cells, 4,760,000; white cells, 11,200; hemoglobin, 80 per cent; young polymorphonuclears, 5 per cent; old polymorphonuclears, 62 per cent; large mononuclears, 9 per cent; lymphocytes, 24 per cent; nonprotein nitrogen, 55 mg., and blood sugar, 84 mg. per hundred cubic centimeters. The Wassermann reaction of the blood was negative.

After three roentgen treatments, the lesions began to show involution.

DISCUSSION

DR. N. TOBIAS: This case is of interest because of its rarity in children. It recalls Wile's interesting work that upset the orthodox ideas regarding xanthoma. In his studies on lipids he found that the amount of cholesterol was not increased in the tumors and that the cholesterol in the blood may even be normal.

LUPUS VULGARIS. Presented by DR. W. C. LANE.

A. P., a white man, aged 38, from the dispensary of Washington University, service of Dr. Engman and Dr. Mook, stated that he had had a sore on his thigh since boyhood that had never healed, although various salves and "lights" had been used. It had caused subjective symptoms. In 1914, a bubo in the left groin was incised. This healed slowly, and later a "breaking-out" similar to that on his thigh appeared in the operative scar. A penile sore in 1917 healed after a few intravenous injections.

On the anterior surface in the upper third of the left thigh there was a slightly raised, flat-topped lesion the size of a small orange. The surface was irregular due to numerous papilliform elevations. The color was a dull coppery red. These papules were soft and doughy, and their grouping and coalescence gave a mamelonated appearance to the lesion. The base showed considerable scarring. A bean-sized, apple jelly-like nodule was seen in the biopsy scar. This was excised for biopsy and showed a typical tubercular structure with numerous giant cells. The Wassermann and Kahn tests of the blood gave negative results.

DISCUSSION

DR. J. GRINDON: The case is undoubtedly lupus vulgaris.

DR. N. TOBIAS: I should suggest the use of the Sauerbrook diet—a salt free diet high in calcium, high in vitamin A and low in proteins. It is used extensively in the treatment for cutaneous tuberculosis in the European clinics with good results.

NEW YORK DERMATOLOGICAL SOCIETY

J. FRANK FRASER, M.D., *Secretary*

Regular Meeting, Dec. 15, 1930

JEROME KINGSBURY, M.D., *President*

LYMPHANGITIS AND SYCOSIS OF THE UPPER LIP. Presented by DR. HOWARD FOX.

H. J. H., was first presented for this condition on April 22, 1930. Dr. Binford Throne suggested that vaccines be injected intradermally into the lesions. This was carried out, and a vaccine similar to that used by Dr. Throne was given twice a week for one month, with slight temporary benefit after the first two or three injections. From this course of treatment no permanent benefit was obtained. The patient was then given autogenous vaccines subcutaneously for one month, which did not give relief.

ULCER OF THE HAND AND FOOT. Presented by DR. HOWARD FOX.

H. J. H. had previously been presented on Oct. 28, 1930, as having a case for diagnosis. Histologic examination of lesions on the hands and feet showed prickle cell epithelioma.

A CASE FOR DIAGNOSIS (LYMPHOGRANULOMA?). Presented by DR. EUGENE F. TRAUB.

In I. M., an Italian housewife, aged 35, an eruption that had started on the arms and forearms five years previously appeared on the breasts a year later. The condition was very itchy, and the patient was treated with salves and by baths at Saratoga without beneficial effect. The eruption on the neck had appeared six months before presentation. The patient said that she had not applied plasters or a hot water bottle to the breasts. She had never received roentgen treatment.

The skin of the neck and of the flexor aspect of the forearms was thickened, with brownish pigmentation and distinct markings. On the left breast there was an area about the size of a dollar, consisting of brownish pigmentation, telangiectasia, scaling and atrophy. There were two similar, more pronounced lesions on the right breast.

The Wassermann test of the blood gave negative results. Examination of the blood showed: urea nitrogen, 13.3; uric acid, 2.96; sugar, 82.3, and chlorides, 536.2.

Biopsy performed on a section from the breast showed dermatitis and that on a section from the forearm showed chronic eczema. The section from the forearm showed an epidermis without rete pegs and an increased number of cells in the granular layer. The basal cells were swollen. There was a dense infiltration of round cells which were scattered throughout the upper third of the corium and were separated from the underlying tissue by numerous dilated blood vessels; a large amount of brown pigment was present in this area of cellular exudate and deeper than this, slight perivascular infiltration about the blood vessels.

The section from the breast showed a normal epidermis with islands of round cells scattered throughout the upper part of the corium. The cells did not approach the layer of basal cells, and the blood vessels in the midcorium and at the periphery of these cells were dilated. The infiltration of round cells was lymphocytic.

DISCUSSION

DR. HOWARD FOX: I do not know what the condition is.

DR. FRED WISE: Like Dr. Fox, I do not know what the condition is, but some time ago I read an article in a German periodical describing a case with

lesions and patches similar to those in this case, and the condition proved to be lymphogranuloma. I should suggest that for consideration in this case.

DR. W. J. HIGHMAN: The microscopic section from the arm showed mostly a deposition of epithelioid cells in the infiltration, which reduced the epidermis to a narrow band. One must consider the diagnoses of atypical sarcoid with atrophy, a discoid type of lupus erythematosus or the condition suggested by Dr. Wise.

PIGMENTATION IN A SCAR FOLLOWING THE REMOVAL OF A NONPIGMENTED PAPILLOMA. Presented by DR. RAY H. RULISON.

Miss M. W., aged 33, a teacher, had had a lesion on the right side of the nose for ten years. It was a skin-colored, raised, soft, nonhairy, slightly lobulated papilloma. There had been no change in the size or character of the lesion for several years.

On Oct. 4, 1930, the papilloma was destroyed by monopolar surgical diathermy; the base was curetted and the raw surface was lightly charred with electrodesiccation. Healing was complete on October 22. The result was a slightly depressed, smooth pink scar.

Forty days after operation and three weeks after the healing was complete, pigment began to appear in the scar, which became pure white in the nonpigmented areas. At presentation, there was a fairly large clump of dark brown pigmentation in the center of the scar with smaller outlying deposits of pigment.

The patient was a blond and had always freckled easily. There had been no unusual exposure to light since the removal of the papilloma.

DISCUSSION

DR. P. E. BECHET: The lesion appeared to me to be a depressed scar with a freckle-like pigmentation. I am not inclined to consider the condition malignant.

DR. E. F. TRAUB: I agree with Dr. Bechet that a freckle has merely developed on the site of the scar of the removed mole. There is, however, a slightly elevated border on the right side of the scar which probably represents part of the original lesion that was not entirely removed, but that should be watched for the possible development of malignancy.

DR. F. C. COMBES: I agree with the others. The patient has freckles on the rest of the face, and I see no reason why there should not be some pigmentation in the scar.

DR. J. J. ELLER: I think that the condition is a nevus pigmentation that appeared as the lesion healed.

DR. HOWARD FOX: It seemed to me, as Dr. Eller said, that this was a nevus that was not entirely removed.

DR. FRED WISE: I think that it is a benign condition.

DR. J. F. FRASER: I do not think that there are potentially malignant nevus cells in this scar. The presence of the pigment will never cause the patient harm.

PAGET'S DISEASE OF THE NIPPLE? Presented by DR. R. H. RULISON.

Mrs. H. T., aged 31, a housewife, was the mother of two children. Late in 1929 she had intended to wean the younger child, but it became ill and she continued to nurse it. The infant was fretful and several times bit her rather severely. In January, 1930, a small area in the nipple became denuded and later crusted. The crusts could be washed off, leaving a raw surface that slowly became larger. The infant was weaned in March.

The patient was treated with mercurochrome-220 soluble, weak silver nitrate, boric acid ointment and balsam of peru without improvement, but the crusting had not occurred since June. The lesion was confined to the nipple and presented a raw, angry surface covered with a mucoid discharge.

The patient was first seen on Nov. 18, 1930, and she was given a mild distillate ointment of coal tar. The lesion seemed to improve for a week or two, but then resumed its former state.

There was no adenopathy, no retraction of the nipple, no induration and no involvement of the areola.

DISCUSSION

DR. P. E. BECHET: I should not suspect Paget's disease, though of course in a persistent chronic eczema that diagnosis must be kept in mind. However, in this particular instance there is a superficial, weeping patch, without retraction of the nipple, ulceration, infiltration or border. For these reasons I regard this condition as eczematoid and not malignant.

DR. E. F. TRAUB: It is almost impossible to say whether there is destruction of the nipple for the other nipple is retracted, and it is difficult to tell by comparison whether a loss of tissue has taken place, but the lesion was certainly infiltrated. There is no way of clinically determining whether or not the process is Paget's disease, and this point should be settled at the earliest possible moment. I think that a biopsy should be performed at once.

DR. F. C. COMBES: I do not see how from clinical examination a definite differentiation between Paget's disease and eczema can be made in this case. The patient seems to have had rational treatment for eczema over a period of several months by means of local applications, without response. I should give the lesion three or four fractional roentgen treatments, and if it did not respond I should perform a biopsy.

DR. FRED WISE: A biopsy should be done immediately. On account of the absence of infiltration, it is questionable whether or not the eczema has been properly treated. I should give the patient roentgen treatment with one massive dose. Then I should take a segment and examine it with the possibility of Paget's disease in mind. I should not perform a biopsy now.

DR. J. J. ELLER: I think that this condition is Paget's disease. The patient has a distinct eruption of the nipple, such as is seen in Paget's disease. A section should be taken from the nipple and serial sections should be examined microscopically. The upper part of the nipple might not show Paget's disease and the other sections might. I had a case in which the patient gave a history of one month's duration. The section showed a typical microscopic picture of Paget's disease. I should not lose time in the case presented by giving the patient roentgen treatment.

DR. W. J. HIGHMAN: I think that one should arrive at a definite appraisal as soon as possible. Dr. Bechet says that he does not suspect Paget's disease. I do not agree with him. One should always suspect Paget's disease in such a case. I do not think one should wait, and I do not approve of the treatment suggested by Dr. Combes and Dr. Wise. I agree substantially with everything that Dr. Eller said. If I were managing this case I should have the patient in the hospital, perform a biopsy of a frozen section and, if necessary, operate immediately.

DR. HOWARD FOX: In saying that he did not suspect Paget's disease, I think that Dr. Bechet meant that he did not favor that diagnosis, since every case of chronic dermatitis about the nipple is indicative of Paget's disease. I am inclined to agree with the suggestion of Dr. Combes and Dr. Wise regarding a trial of the roentgen rays and then, if no substantial benefit results, to perform a biopsy.

DR. J. F. FRASER: On clinical grounds it is impossible to decide whether the condition is Paget's disease of the nipple or eczema. A biopsy should be performed. Cutting out a piece for microscopic examination is a safe procedure. Palpating the lesion is probably more dangerous. When the vessels are cut, the flow is outward and the tendency is to wash away any loose cancer cells rather than to carry them by the blood stream to distant organs. Mastectomy should be done as soon as possible if the histologic report is positive for malignancy. The reasons for early operation are: (1) The clot that is formed may produce a

favorable focus for the growth and dissemination of cancer cells; (2) the healing process following the biopsy may constitute an additional source of irritation, and irritation is unquestionably an etiologic factor in the causation of cancer.

I disagree with the suggestion that roentgen therapy should be tried first. Whether the condition is Paget's disease or eczema, massive doses of roentgen rays may clear it up temporarily. Dr. Sequeira related a sad experience with roentgen therapy in three cases. The treatment was followed by a clinical cure, but all of the patients died within two or three years from carcinoma of the breast.

DR. HOWARD FOX: I should like to ask Dr. Fraser what he considers a safe interval between the performance of the biopsy and a subsequent operation on the breast? In performing a biopsy, which would he advocate, the use of the knife or surgical diathermy?

DR. J. F. FRASER: In reply to Dr. Fox's questions: The safest interval is the shortest time possible after a histologic diagnosis of malignancy, which need be only a few hours if paraffin sections are used. If the biopsy is performed in the morning, the pathologist's report should be available in the afternoon of the same day. Reports from frozen sections can be obtained in a few minutes, but frozen sections are not always satisfactory. I advocate the use of the knife in preference to surgical diathermy, because there is less destruction of tissue and consequently a clearer histologic picture.

DR. W. J. HIGHMAN: No one knows when Paget's disease starts, so the right time to remove it is the second after it is a proved case. If one waits two weeks, one might as well wait a month.

DR. P. E. BECHET: Dr. Wise has stated exactly what I had in mind when I first discussed the case. I agree with him absolutely. I cannot see that this case is anything but eczema of the nipple, and I should treat it as such rather than as Paget's disease.

DR. E. F. TRAUB: Apparently the point that I wanted to make was misunderstood by some of the members. I thought that the nipple was decidedly infiltrated. There is no infiltration of the surrounding tissues, but the area of the nipple is certainly definitely thickened, eroded and oozing. The point that I made about the biopsy was that I do not think that a diagnosis can be made without an examination of sections, and that this should be done at once to determine the correct diagnosis.

DR. HOWARD FOX: It seems to me that there is a practical question to consider. Theoretically, I agree with Dr. Highman that the breast should be removed as soon as it is found to be cancerous; but there are many women who would not consider an operation unless it was definitely proved that they had cancer, and in this case a biopsy would be required and a wait of a week or so would not be dangerous. One cannot easily induce people to go into a hospital and be ready for an immediate radical operation.

DR. R. H. RULISON: I am delighted with the discussion, for the case has been on my mind a good deal. This patient has been under the observation of her family physician for ten months. I saw her only two or three weeks ago. She has two small children and cannot be hospitalized until there is a proved reason for it. Even a biopsy on the nipple is a deforming operation and not one that one would like to do. I was interested in the suggestion that it was safe to wait a week after a biopsy before doing a radical operation, since this would make possible a delay in sending this patient away from her children. Dr. Wise suggested that I give her a few doses of roentgen rays. I am inclined to give this patient three or four small doses of roentgen rays and, if there is no marked or permanent improvement, then to do a biopsy, and if anything malignant is found, to send her to the hospital and have a mastectomy performed. So far as I can make out, that is about the consensus on the case this evening.

DR. J. J. ELLER: I think that a biopsy of the nipple should be done with a punch. As for the rarity of the disease, during the past year in private practice

I have had three cases that have been confirmed by microscopic examination, and a study of two of these has been reported in the literature.

SUPPLEMENTARY REPORT.—Fractional treatments with the x-rays were administered to the nipple, amounting to a total dose of 1¼ skin units, between December 22 and January 16. There was no definite improvement.

On January 23, a biopsy was made with a skin punch from the edge of the nipple, including some of the areola. The specimen was examined by Dr. Fraser and Dr. Smith of Cornell, and a diagnosis of Paget's disease of the nipple was made.

BROMODERMA. Presented by DR. HOWARD FOX.

A. M., a married woman, aged 36, had taken medicine of unknown composition for six months. An eruption occurred three months before presentation. It consisted of a serpiginous patch about 6 inches (15.24 cm.) in diameter on the calf of the right leg; it was a horseshoe-shaped, superficially ulcerated and crusted area with a raised advancing border, suggesting either blastomycosis or a nodular syphilid. These two diagnoses were rendered improbable from the highly inflammatory character of the lesions which were painful and very tender, causing the patient to limp when walking.

Examination of the urine for iodine gave negative results, but with the Belote test positive results for bromine. Information was later obtained that the medicine she had taken contained bromides. She had been given one intravenous injection of 200 cc. of physiologic solution of sodium chloride, and was steadily improving.

TELANGIECTATIC NEVUS. Presented by DR. PAUL E. BECHET.

B. L., a girl, aged 9, was presented with only a tentative diagnosis of telangiectatic nevus because of the many peculiarities presented by the eruption.

The mother stated that it had begun when the child was 1 year of age. The development of the lesion had been slow but progressive. It consisted of a gyrate, serpiginous telangiectasia distributed symmetrically over the nose and cheeks. In a strong light there were undoubtedly a few areas of superficial atrophy. The dilated arterioles were remarkably serpiginous, not unlike angioma serpiginosum. The lesion had never been treated.

DISCUSSION

DR. C. M. WILLIAMS: I do not think that the condition is a nevus, but that a genuine change is going on under the skin. There is an area on each side of the nose where the level of the skin is distinctly depressed. There is some disease of the blood vessels which is not nevus, but I do not know what it is.

DR. W. J. HIGHMAN: I agree with Dr. Williams, but I think that the patient ought to be watched for the development of angioma serpiginosum.

DR. E. F. TRAUB: I do not know how to connect the telangiectasia present with what the lesion as a whole suggested to me, but the possibility that this condition was a beginning case of scleroderma should be kept in mind.

TUBERCULOSIS AND LEUKOPLAKIA OF THE BUCCAL MUCOSA. Presented by DR. FRED WISE.

W. N., aged 44, presented himself at the Skin clinic of the New York Post-Graduate Hospital with a condition of the mouth which he said had been present for two months. The left buccal mucosa presented an elongated fissure, extending from the upper lip downward and backward for 1.5 inches (3.81 cm.). The mucosa on both sides of the fissure showed definite leukoplakia that merged into normal mucous membrane. On palpation, the lesion felt thickened and indurated. Externally, the left cheek presented visible swelling, and at the left angle of the jaw there was a sebaceous cyst. The buccal mucous membrane on the right side at the junction of the upper and lower teeth presented evidence of leukoplakia.

The patient gave a history of smoking about twenty cigarets daily. He said that he had not had syphilis, and two recent Wassermann tests gave negative results. Examination of the lungs gave negative results. The patient had received treatment with radium.

At the time of admission the following diagnoses were considered: (1) leukoplakia with malignant degeneration and (2) tuberculosis. The following biopsy report was given by the pathologist: prickle cell epithelioma; possible tuberculosis.

DISCUSSION

DR. E. F. TRAUB: I think that it is impossible to make a clinical diagnosis this evening as the massive dose of radium that the patient has received would produce a large portion, if not all, of the superficial ulceration that is present.

DR. W. J. HIGHMAN: Tuberculosis was present, but in the slide presented tonight there was no evidence of epithelioma.

DR. J. J. ELLER: I am relying on the microscopic diagnosis. I do not know which one to believe, but we all know that it is not rare for an epithelioma to develop on a tuberculous lesion. The patient was treated with five tubes of radium as a plaque, each one filled with 25 millicuries of radon, and the reaction has not as yet passed out of the lesion. It will take some time before one can decide on the result of the treatment with radium.

SARCOID (DISSEMINATE TYPE). Presented by DR. F. C. COMBES.

P. P., a Negress born in the United States, aged 25, gave the history of the appearance of an extremely pruritic dermatosis that reached its height in about ten days. Her general health was excellent, and she had had no constitutional disease of consequence. The eruption as presented was of about fourteen weeks' duration; it was generalized, with the exception of the face, palms and soles. It consisted of approximately 200 well defined, elevated lesions, with a tendency to ovoid shape, the long axes lying in the direction of the lines of cleavage of the body. The lesions were somewhat darker than the normal skin, and the visible cutaneous markings on the surface were exaggerated. The surface was flat, somewhat verrucous, and in many instances it was covered with a fine powdery scale. The lesions were firm, and presented no evidence of caseation, ulceration or an acute inflammatory process. Under the breasts they had fused to form large flat plaques with polycyclic borders and a velvety violaceous surface. On the back also many of the lesions were confluent. There were no objective signs of itching, and the patient stated that this symptom had gradually disappeared. There was no adenopathy.

The Wassermann test of the blood gave negative results on two occasions. The Pirquet test gave negative results. The fixation test of the blood for tuberculosis gave negative results. Examination of the blood showed: erythrocytes, 5,100,000; hemoglobin, 80 per cent (Tallqvist); polymorphonuclears, 71 per cent; large lymphocytes, 15 per cent; small lymphocytes, 5 per cent; large mononuclears, 8 per cent, and eosinophils, 1 per cent. Roentgen examination of the chest and hands gave normal results.

The condition had shown gradual improvement during the administration of $\frac{1}{30}$ grain (0.00216 Gm.) of arsenous acid three times a day.

The histologic diagnosis of atypical evidence of tuberculosis and probably a disseminate sarcoid was made.

DISCUSSION

DR. HOWARD FOX: I saw the patient at the clinic, and from the clinical standpoint the most plausible diagnosis was lichen planus. We were all surprised to hear the histologic report that the condition was probably sarcoid.

DR. W. J. HIGHMAN: The histologic evidence indicates sarcoid. It is not typical, but sufficiently indicative of sarcoid to warrant this interpretation of the slide.

DR. J. F. FRASER: I agree with Dr. Highman's interpretation of the histologic picture.

DR. F. C. COMBES: The lesions are now flatter than they were before. They were vegetative at one time, but they have receded considerably in the last month.

PITYRIASIS ROSEA SIMULATING ERYTHEMA MULTIFORME. Presented by DR. PAUL E. BECHET.

D. G., a woman, aged 38, stated that the eruption had been present for two weeks. Rounded spots, with an occasional inner ring, strongly suggestive of erythema iris were scattered over the trunk and limbs. However, they were not vesicobullous; on the contrary, they presented the cigaret paper-like center characteristic of pityriasis rosea. There was a large herald patch on the thigh.

PAPULONECROTIC TUBERCULID: EXTENSIVE INVOLVEMENT OF THE FACE. Presented by DR. PAUL E. BECHET.

M. K., a young woman, aged 18, had first noticed lesions on the arm and face ten years previously, at the age of 8. The disease had not only persisted since then, but it had greatly increased in severity. The face was literally covered with pitted cicatrices and many active red lesions with necrotic centers. On the arms and legs the lesions were discrete, but they presented the characteristic violaceous nodule with necrotizing center. A test with tuberculin proved negative, but the lesions had been so characteristic that, despite this fact, no other diagnosis had been entertained.

MYCOSIS FUNGOIDES. Presented by DR. FRED WISE.

H. B., a Russian Jew, aged 69, presented himself at the skin clinic of the New York Post-Graduate Hospital on Nov. 18, 1930, with a condition of the skin of two years' duration. On the trunk and extremities were numerous plaques palm-sized and larger; they were pink and red and infiltrated; their borders faded into normal skin. The anterior abdominal wall presented a flattened infiltrated mass about 1 inch (2.54 cm.) in diameter. Several of the areas had been treated with salves, and they were erythematous and scaly. The itching was moderate.

DISCUSSION

DR. W. J. HIGHMAN: I agree with the diagnosis.

DR. C. M. WILLIAMS: I think that the condition is mycosis fungoides. It is not only dry but itchy and scaly, and lumps are developing. An ulcer is also forming on the right flank, and there are several places in which nodules are beginning to develop.

DR. J. F. FRASER: I agree with the presenter's views, but the clinical diagnosis should be confirmed by microscopic examination.

SENILE CONDITION OF THE SKIN SUGGESTING THE APPEARANCE OF LEPROSY. Presented by DR. HOWARD FOX.

D. B., a Roumanian farmer, aged 57, an immigrant at Ellis Island, had previously spent six years in the United States, beginning in 1914. He was said to have suffered from some severe generalized condition of the skin as an infant. The eruption exhibited had been present as long as he could remember. It was difficult to obtain a proper history. The condition of the skin was confined to the face, being most noticeable on the forehead, the nose and the malar regions. It consisted of soft, closely aggregated, yellowish, pea-sized, flattened elevations with corresponding furrows and apparently some pitted scars, suggesting a former variola. There was marked alopecia of the eyebrows. At a distance the nodular appearance suggested leprosy, though the lesions did not cause the typical leonine

expression, and the lobules of the ears were free. The possibility of leprosy had been previously considered, and a nasal smear was made, but showed no bacilli. Anesthesia was not present on any part of the body; enlargement of the nerves most often affected by leprosy and macules indicative of that disease were not present. Apparently there was a slight atrophy of the first interosseous muscle of one hand and a slight wrinkling of the skin of the dorsal surface. From the clinical examination, apparently leprosy could be excluded. The patient was a man of medium size and apparently in good health.

Histologic examination excluded the possibility of leprosy. The report was as follows: "The lesion is not inflammatory. The epidermis shows no noteworthy changes. The elastic tissue takes basic but not acid stains. Changes of this sort in elastic tissue are generally found in senile skin. Similar changes are seen in pseudoxanthoma elasticum. Conclusion: The specimen described is one of senile skin."

DISCUSSION

DR. W. J. HIGHMAN: I saw the section the other day in my routine work, without having seen the patient. It showed no changes other than those in the elastic tissue, which took the basic stain of "elastin," as Unna calls it. In other words, the skin showed regressive changes of the elastic tissue. When the elastic tissue is chemically unchanged, the picture of pseudoxanthoma elasticum is produced. In the senile skin, the elastic tissue is chemically changed. In either instance it shows as a yellow discoloration in the skin. Either the man had smallpox when he was young, which would account for the pitting, or changes occurred in the elastic tissue that rugated the skin. But the condition is not pseudoxanthoma elasticum. I think that the skin is senile.

DR. J. J. ELLER: I think that Dr. Highman has covered the case, and I agree with his remarks.

DR. FRED WISE: I agree that the condition is senile degeneration. The condition has been described by the Germans in the *Archiv für Dermatologie* as a condition that occurs on the back of the neck in old men.

DR. C. M. WILLIAMS: I think that the condition is a senile change. I did not see pits of smallpox, but many senile creases. I think that that is the whole story.

DR. E. F. TRAUB: I did not see any trace of the sequelae of smallpox.

DR. HOWARD FOX: I was certain that the diagnosis of leprosy could be ruled out. In this apparent nodular formation with pits suggesting smallpox, the elevations were soft and not like the nodules of leprosy, and the patient showed no other signs of that disease. I think that Dr. Highman's interpretation of the case is probably correct.

PEMPHIGUS. Presented by DR. E. F. TRAUB.

The patient had been shown at the November meeting with the diagnosis of pemphigus. That diagnosis was questioned, and dermatitis herpetiformis which of course had been considered and lupus erythematosus were suggested as possibilities. Two phytopharmacologic examinations of the blood, made at intervals of three weeks had been reported by Dr. Pels as showing toxicity. The test for potassium iodide had also indicated the diagnosis of pemphigus. A slide was submitted for examination, and this ruled out the possibility of lupus erythematosus. New crops of vesicles were constantly appearing, and the area of the eruption was gradually spreading.

DISCUSSION

DR. C. M. WILLIAMS: The case is very interesting; it is not typical, and yet I think that the diagnosis will prove to be correct. The lesion on the eyelid and the report from Dr. Pels give that impression. Most of such cases that we have discussed have turned out to be pemphigus, although the diagnosis may not have

been made at the time. The itching does not indicate pemphigus. I cannot account for the lesion on the right side of the forehead. That bulging mass does not look like pemphigus.

Dr. R. H. Rulison: I think that the condition is an atypical case of pemphigus.

Dr. Howard Fox: We all agree that it is impossible to make a definite diagnosis now. The positive result of Pels' test and the loss of weight indicate pemphigus, but the itching is against it. As to the age of patients with pemphigus, at a recent meeting of the Minnesota Dermatological Society I saw a case of pemphigus in a woman of 80. I had never seen this disease in a person of such advanced age.

Dr. W. J. Highman: Clinically, the case impresses me as being Duhring's disease, as it did a month ago; but one knows that such cases are difficult to diagnose. If the Pels test shows pemphigus, I should favor that diagnosis.

Dr. J. J. Eller: I agree with Dr. Fox that it is impossible to make a diagnosis today. The Pels test showed a high degree of toxicity, but this may be found in other conditions. I have a patient who suffers from ioderma who showed a 65 per cent toxicity, as reported by Dr. Pels.

Dr. Fred Wise: I agree with Dr. Highman. I do not think that the condition is pemphigus, as atrophy of the skin is not present in this disease or in Duhring's disease. The reason why I think that the condition is lupus erythematosus with bullous changes is that at the Post-Graduate Clinic there is a patient with exactly the same type of lesions, and the histologic section from a lesion outside the bullous area showed the histologic changes of lupus erythematosus. Therefore, I think that there is a possibility of that disease.

Dr. E. F. Traub: I presented a slide of a section that was taken at a distance from any bleb but in the general area of the eruption where there apparently was atrophy, and the laboratory returned the diagnosis of pemphigus. Two Pels tests were made on this patient, both of which gave toxic results. Not all of these tests prove correct, but certainly they were right in most of the cases in which I have submitted samples. The fungating lesion on the temple has developed only in the last few days and may be the result of the ingestion of iodides.

Report on Cases Previously Shown. Presented by Dr. F. C. Combes.

A young girl with lesions under the breasts had been presented at the last meeting and at the Academy of Medicine. A tentative diagnosis of nevus or urticaria pigmentosa had been made. The microscopic examination showed nevus and large diffuse areas of cells of the endotheliomatous type but without the characteristic grouping seen in endothelioma.

Another patient had an annular macular syphilid, and the biopsy showed a fixed erythema, which coincides with Unna's description. The condition was syphilis of the vasomotor nerves, and it did not show the characteristic infiltration of syphilis in the tissues.

DISCUSSION

Dr. Howard Fox: I had occasion to present the first case of this kind in the United States. I am sorry that I did not see Dr. Combes' patient last month. Dr. Combes spoke of the improbability of the condition being a syphilitic manifestation after so many years.

Dr. F. C. Combes: I had said that this condition was not a relapsing secondary eruption but rather a vasomotor manifestation accompanying cerebrospinal syphilis.

Dr. Howard Fox: This condition can occur after any number of years. It is interesting to note that nearly all of these cases have been seen in women.

SYCOSIS.

Dr. Howard Fox inquired about the case of sycosis previously shown by Dr. Throne. He asked about the results of treatment with intradermal injections of vaccine and whether anyone had seen favorable results from such treatment.

DR. P. E. BECHET: In a similar case negative results were obtained after 100 intradermal injections.

CHICAGO DERMATOLOGICAL SOCIETY

Regular Meeting, Dec. 17, 1930

CLARK W. FINNERUD, M.D., *President, in the Chair*

PEMPHIGUS OR LEUKOPLAKIA? Presented by DR. E. A. OLIVER.

A white man, aged 43, was first seen on April 21, 1930. On either side of the mouth on the buccal mucosa opposite the last molar teeth there were two patches the size of a quarter. These were much inflamed and irritated, and covered with a grayish pellicle. On the mucous membrane of the lower lip there was another superficial area. Examination also revealed an erythematous scarlatiniform eruption on the chest and the abdomen, which was evidently caused by an injection of neoarsphenamine given by another physician several days previously. The Wassermann test of the blood and the examination for Vincent's organisms gave negative results.

Since April 21, he had been under constant observation. The lesions had been painted with silver nitrate and mild silver protein, and recently he had been using a sodium perborate paste. He did not improve under treatment with a solution of potassium arsenite, and he had had rather intensive treatment with tryparsamide. The patches had refused to yield to any sort of treatment.

DISCUSSION

DR. O. H. FOERSTER: In regard to the possible diagnosis of pemphigus that was offered, I could not see any bullous lesions of pemphigus or remains of bullae. I saw a leukoplakic process not limited to the buccal mucosa but extending on to the gingival border and the alveolar process. The patient had many amalgam fillings in his teeth, the mouth was septic and the teeth were out of line. I should be inclined to believe that we are dealing with a response by the mucosa to a septic condition of the mouth resulting from lack of care.

DR. E. A. OLIVER: Because of the irregularities of the borders of the lesions and their extreme soreness and superficiality in a man whose health had rapidly become worse, I was more inclined to think that this was a localized pemphigus.

(Since he was shown at this meeting, the patient has improved a great deal. Dr. Potts, an oral surgeon, scaled his teeth, and under treatment with a soothing mouth wash the inflammation has subsided. The most probable diagnosis now is leukoplakia with a superimposed infection. More cultures are being made.)

A CASE FOR DIAGNOSIS (LUPUS ERYTHEMATOSUS? PARAPSORIASIS?). Presented by DR. W. A. PUSEY and DR. L. F. WEBER.

In T. S., a man, aged 55, a patchy discoloration developed during April, 1930. The patient's general health was good. There was no history of the ingestion of drugs. The Wassermann reaction of the blood was negative. There were no subjective sensations. The eruption was persistent, showing hardly any tendency to undergo spontaneous involution.

He had irregular patches varying in size from ½ to 2 inches in diameter on the trunk and extremities. Most of the lesions were round; only a few were

oval. The color varied from red to dark brown. A few of the patches were so delicate as to appear to be mere stains. Slight scaling was present in many of them, the scales being small and adherent. There were no elevation of the lesion and no infiltration of the skin. The mucous membranes did not show any lesions.

DISCUSSION

DR. UDO J. WILE: I have never before seen a case like this. There were some lesions that suggested a very superficial form of erythematous lupus.

DR. F. E. SENEAR: I feel as Dr. Wile does; I have never seen anything resembling this case. One interesting point was that the patient had lesions on the scalp as well as on the body, and I think that those on the scalp were the only ones that showed any degree of activity. I felt that I could distinguish some definite follicular plugging in the lesions in the scalp, and that particularly inclined me toward a diagnosis of lupus erythematosis.

DR. O. H. FOERSTER: I have nothing to offer, except a suggestion that the patient may have been embarrassed by the consideration of a possible dermatitis medicamentosa.

DR. L. F. WEBER: I questioned the man about drugs on several occasions and was never able to obtain a history of the injection of drugs. Lupus erythematosus was one of the diagnoses that we considered. One consideration that I had in mind was that this condition might fit in with some of the cases of parapsoriasis that have been described. I refer to some cases that Crocker described in 1905, which were later put into the group of parapsoriasis.

A CASE FOR DIAGNOSIS (SEBORRHEIC DERMATITIS?). Presented by DR. S. W. BECKER.

A woman, aged 67, complained of an eruption about the mouth, of one and one-half years' duration. The disease began as an erythematous plaque on the chin just below the left oral commissure, several weeks following extraction of the teeth. It spread to the vermilion borders and to both lips and the chin. It was treated by roentgen rays, ultraviolet rays and local applications.

The general physical examination gave negative results. The red and white blood cell counts were normal. On the lips and especially on the chin was a well defined and slightly elevated erythematous plaque with a distinct yellowish hue. Portions of the lesion showed atrophy and telangiectasia.

Histologic study showed superficial degeneration of the collagen, with moderate infiltration of round cells.

DISCUSSION

DR. E. P. ZEISLER: I thought that this was a seborrheic dermatitis about the mouth. I have seen similar eruptions resulting from the use of gold sodium thiosulphate.

DR. CLEVELAND J. WHITE: The pigmentation around the mouth suggested to me the possibility of a fixed exanthem caused by a medicinal agent like phenolphthalein.

DR. M. H. EBERT: I thought of the possibility of some type of lupus erythematosus.

DR. E. A. OLIVER: I thought that the case was suggestive of a superficial type of lupus erythematosus, especially about the chin, lips and mucous membrane.

DR. S. W. BECKER: We felt that some of the telangiectasia was caused by the roentgentherapy that she had received.

DR. O. H. FOERSTER: This patient had several grayish patches on the tongue and none on the buccal mucosa. I think that the condition could be brought into agreement with a diagnosis of very superficial erythematous lupus of the telangiectatic type.

A Case for Diagnosis (Scleroderma?). Presented by Dr. H. Rattner.

M. K., a man, aged 28, a painter, had had a pigmentary disease for five years. The familial and past histories were irrelevant except for an attack of influenza sixteen years previously, and poison-ivy dermatitis six years previously. He had a grayish-brown hyperpigmentation involving chiefly the right half of his body and the extremities. It began as a yellowish spot on the flexor surface of the right wrist, which remained unchanged for two years and then began to change color gradually until it reached its present hue. It spread by extension to the present sites, affecting the trunk on the right side from the spine to the midline of the abdomen, the outer surfaces of the right forearm, the entire right arm, the right buttock, and the outer surface of the right thigh and leg down to the ankle. There were a few recent, scattered patches the size of a coin on the left side of the body, the chest, the buttock and the thigh. The exposed surfaces were not involved. The patches were irregular in shape and size, and the pigment was in places mottled, reticulated and diffuse. Scattered among the patches were distinct tiny areas of atrophy. The lesions did not fade on pressure. There was no thickening of the skin. There had never been any subjective symptoms. The general health of the patient was good, except for constipation for which he took citrate of magnesia and a proprietary preparation. There had been no other internal medication. The results of the general physical examination were negative. The blood pressure was 134 systolic and 78 diastolic; the blood picture, urine and Wassermann reaction of the blood were negative. He had had a few intravenous injections of sodium thiosulphate and some local applications of coal tar and salicylic acid ointment, but they were without effect.

Biopsy showed a thin, non-nucleated scale. The basal layer of the epidermis contained many brown pigmented granules. In the upper part of the corium there were a few scattered brown chromatophores and a slight perivascular infiltration of round cells. Weigert stain showed that the elastic fibers just beneath the epidermis were destroyed in places.

DISCUSSION

Dr. Udo J. Wile: I think that this is a case of a superficial, unusual type of scleroderma. There is one definite plaque in the nape of the neck, which, if seen alone, would probably be diagnosed as an involuting patch of morphea. Also there is a characteristic patch on the abdomen.

Dr. James H. Mitchell: I am inclined to favor that diagnosis also. A great amount of pigment can develop anywhere in circumscribed scleroderma. I had occasion to observe that recently in a patient with a patch on the back. The patient was seen on two occasions about nine months apart, and the amount of pigment that developed during that period was amazing.

Dr. H. Rattner: That was our first impression when the patient came into the office, and we made a tentative diagnosis of scleroderma.

Dr. Ruben Nomland: It seemed to me that the elementary lesion was one no larger than a pinhead. It was atrophic, and I do not see how anyone can make a diagnosis of scleroderma in cases in which the primary lesion is atrophic. If it was guttate scleroderma, it certainly was not like the typical picture. The microscopic picture did not show the necessary changes.

Dr. H. Rattner: The newer lesions apparently are composed of pigmentation. I did not see the early ones and there have been no new lesions since the patient first came under observation four weeks ago.

Dr. Udo J. Wile: I was not able to substantiate Dr. Nomland's observations. It is difficult to understand how the large pigmented patches could have started with the lesions the size of a pinhead. There are cases of localized scleroderma that are not perceptible until the atrophic stage is reached. They are very superficial and insignificant. All of the characteristics of these lesions point to scleroderma. It is perfectly evident, however, that it is an unusual scleroderma, but it does fit in with the characteristics of that disease. As Dr. Mitchell pointed out,

hyperpigmentation is occasionally one of the distinguishing features of morphea. I saw one case in which a patient was left with an absolutely negroid skin across the abdomen. I am sure that there are cases in the literature with as much pigmentation as this patient shows.

CONGENITAL ECTODERMAL DEFECT. Presented by DR. F. E. SENEAR and DR. M. R. CARO.

A white girl, aged 16, had had a disease of the skin since birth. She was mentally subnormal and could give no information. It was learned, however, that she had a living sister and father and that her mother was dead, but nothing was known of the condition of the skin in these members of the family. The patient stated that she did not perspire.

The changes in the skin were generalized, but were most pronounced on the face, thighs and forearms. The turgor of the skin was good and the changes seemed to be superficial. There was a reticular atrophy giving rise to many fine wrinkles, at the base of each of which the skin was thin, erythematous and scarlike.

The scalp was involved by a diffuse erythema and fine, dry scaling, and on the vertex there was a patch of scarring alopecia, the size of a dollar.

There were malformations of the fingers, with fleshy union of the last two fingers of the right hand and of the left index finger and the middle finger. Several finger-nails showed peripheral dystrophy and fissuring. On the left foot the last three toes were joined. On the right foot there were only a large great toe (composed of three toes), a single little toe, and a narrow toe between them.

The teeth showed poor development and there was a high arched palate.

DISCUSSION

DR. M. H. EBERT: I agree with the diagnosis. When I first looked at the patient at a distance I thought of Hutchinson's angioma serpiginosum, but on closer scrutiny I realize that this is not an instance of that disease. The patient had many different types of lesions.

DR. E. P. ZEISLER: Was this case presented as the hereditary form of telangiectasia or as a congenital ectodermal defect? There are some congenital abnormalities present but not the complete clinical picture of an ectodermal defect.

DR. MAX S. WIEN: This case is similar to one that was shown at the meeting held in May, 1930, (Senear, F. E., and Caro, M.: Generalized Telangiectasis, ARCH. DERMAT. & SYPH. **23**:181 [Jan.] 1931). In that case, generalized telangiectasia was present, and the neurologists suggested that these lesions occur in connection with tuberous sclerosis of the brain. In that instance capillary microscopy revealed hyalinization of the peripheral vessels.

DR. RUBEN NOMLAND: Dr. Goeckerman reported a case of "congenital ectodermal defect" in which there was quite a different picture with diseased nails and skin, and a saddle nose, but so far as I know there was no telangiectasia. The patient shown today has telangiectasia of the type that has been shown twice, by Ebert and by Wien. Apparently the same mental defect was present in the latter cases as in the case under discussion.

DR. S. W. BECKER: I think that it is not a typical congenital ectodermal defect, although the patient presents many defects. The only factor that I could see that might be ectodermal was the ichthyotic condition of the skin, probably due to the glandular structures. I think that the ectodermal defect is simply part of the general disturbance.

DR. MARCUS R. CARO: One point in which the clinical observations do not agree with the history given was that the patient stated that she did not perspire. I noticed that her hands were clammy after the nervous stimulation incident to being examined.

DR. F. E. SENEAR: I shall be glad to accept Dr. Zeisler's correction. We do not have in mind at all the type of ectodermal defect that Dr. Nomland has described and that has appeared so often in the literature. We might say that it is a defect with telangiectasia, and eliminate the ectodermal phase.

A CASE FOR DIAGNOSIS (LYMPHOBLASTOMA?). Presented by DR. H. M. HEDGE.

M. H., a white girl, aged 6, was in perfect health until a year before presentation, when her hands and feet began to show a definite erythema which progressed for about six weeks. The erythema attained a definite border about 3 cm. above the wrists and about the same distance above the malleoli where it became stationary. It remained in this state until October, 1930, when it again became active and spread upward to the knees and elbows. The lesions were not painful, and itching was negligible.

She was first seen at the clinic of the Northwestern University Medical School in May, 1930. The Wassermann and Kahn reactions were both frankly negative. A roentgenogram of the chest showed no visible signs of tuberculosis. The basal metabolic rate was between +19 and +24. The blood count showed 4,730,000 red cells, 5,450 white cells and 75 per cent hemoglobin. The differential count showed: lymphocytes, 39 per cent; large mononuclears, 2 per cent; neutrophils, 57 per cent; eosinophils, 4 per cent; no basophils. There was a uniformity of shape and size of the red blood cells.

The case was presented with a tentative diagnosis of glandular disturbance, with a possibility of a beginning toxic dermatitis in the group of lymphoblastomas.

The patient had been given five roentgen treatments, thyroid extract by mouth, and bland ointments and lotions locally but had received little benefit.

DISCUSSION

DR. J. H. MITCHELL: My impression was that this was probably a case of pityriasis rubra pilaris. There were a few lesions over the proximal phalanges that suggested that disorder. I recall a patient whom Dr. Ormsby and I saw many years ago in whom the lesions on the hands were much like this. They were symmetrical and stopped short on the flexor surface of the wrist. The child had badly infected tonsils and after the removal of these, the eruption cleared up. Without any further data in this case I should favor a diagnosis of pityriasis rubra pilaris.

DR. H. M. HEDGE: One of the interesting features of this case was that before the lesions appeared the skin was unusually smooth. The child had never had infantile eczema or an eruption of any sort. Two other children in the family have a very clear skin, as does the mother. This disease came on suddenly and I favor the belief that it falls in the group of lymphoblastomas.

ERYTHEMA INDURATUM WITH TUBERCULOUS CERVICAL ADENITIS. Presented by DR. E. P. ZEISLER.

A woman, aged 36, showed typical bilateral Bazin's discoid lesions of the calves, of three months' duration. Since she was 2 years of age, she had had tuberculous glands of the neck, which were operated on in February, 1930. At the time of presentation, the treatment included ultraviolet light irradiation of the glands of the neck.

ERYTHEMA INDURATUM (?). Presented by DR. F. E. SENEAR and DR. MAX S. WIEN.

An obese Russian woman, aged 39, was shown in 1927 (Senear, F. E., and Wien, M. S.: Erythema Induratum Thrombosis Colliquativa, ARCH. DERMAT. & SYPH. **16**:364 [Sept.] 1927) at which time she presented multiple infiltrated hard

nodules about 2 inches (5 cm.) in diameter scattered over both legs and on the buttocks. At that time some of the lesions were crusted, and one on the left leg was a superficial ulcer with ragged edges. The patient first noted painful nodules on the buttocks in 1920, and the lesions first appeared on the legs about 1924. She had been under observation since 1927 and during that time had never been entirely free from ulcerative lesions on the calves. She received neoarsphenamine, silver neoarsphenamine, gold sodium thiosulphate and bismuth by injection, with mercury and potassium iodide by mouth in the intervals, but did not experience complete relief from the occurrence of ulcerative lesions on the legs. Her general health had been good. She had three living children and had had two miscarriages. The Wassermann and Kahn tests of the blood were repeatedly negative. Her mother had died of tuberculosis at the age of 35.

Two months previously there had been practically complete involution of all the ulcerative lesions after six weeks of treatment in the hospital, including complete rest in bed and local wet dressings. The involuted lesions left bluish thickened scars at their sites. New lesions appeared at the margins of the healed areas before she was discharged from the hospital, and these lesions were seen on both calves as irregular ulcers of varying size and depth with ragged edges and a base of granulation tissue. The lesions were painful and kept the patient awake at night.

Histologic study of an excised nodule, removed in February, 1927, revealed in the section an infiltration of the fat and of the fibrous tissue by round cells, with several areas showing tubercles and many epithelioid cells. A histologic diagnosis of fibrocaseous tuberculosis had been made at that time.

DISCUSSION

DR. E. A. OLIVER: I think that Dr. Zeisler's case was a true erythema induratum. I have observed the other case several times with Dr. Wien, and I am inclined to believe that it is a low grade tuberculous process and not an erythema induratum.

DR. UDO J. WILE: If I had not heard from Dr. Senear that in his case, many years ago, a specimen from a nonulcerative lesion at biopsy showed a tuberculous structure, I should have suggested that the lesions looked more like those of infarcts of the skin. It may well be that a distinction on clinical grounds should be made between the type of erythema induratum that does not ulcerate and the ulcerative type, such as is seen in Dr. Wien's patient. In the last analysis, however, there is not so much difference for they are both tuberculous. Our present knowledge of the many mutation forms that the tubercle bacillus can make in the skin seems to me to raise questions that are of academic interest but not vitally important.

DR. F. E. SENEAR: I might clarify the situation a little by saying that the first lesions on the buttocks developed about ten years ago, seven years before we saw the patient. These had largely involuted, had never broken down, but left fibrous nodules each of which produced a deep dimple. When we first saw the patient, she had a number of subcutaneous nodules of the calves which were very firm. At this time she had some superficial plaques which had broken down and which showed clinically typical erythema induratum with the ulceration seen in that type of case. Those lesions healed under treatment with gold and various other therapeutic measures, and then she had a recurrence. When she was put in bed, the remaining ulcers healed entirely, but during the last few months all the lesions have been entirely different in character from those that we first saw. They have been of a more sluggish type and I feel that at present they are on a tuberculous basis but that perhaps some secondary factor, such as a streptococci or low grade pyodermic infection, has entered in. I had not thought of infarcts, but they possibly explain the present picture.

DR. E. P. ZEISLER: I brought in the case of erythema induratum, which is a typical one, for comparison with the other case, which is unilateral and in which the ulceration is much deeper. It might fit in with what the French call "scrofulous gumma." The patient should have mercury and iodides, and the therapeutic test should be given before syphilis can be ruled out entirely.

MYXEDEMA OF THE LEGS. Presented by DR. E. A. OLIVER.

A. R., aged 42, was admitted to the Cook County Hospital on Nov. 5, 1930, with a corneal ulcer. There was swelling of both legs which began about three months after a thyroidectomy, which was done on Aug. 5, 1928. The swelling occurred first in the right leg and since then had gradually increased, most rapidly at the shoe line. No subjective symptoms had been noted at any time. The white blood cell count was 9,400. The differential count showed: polymorphonuclears, 45 per cent; lymphocytes, 44 per cent; mononuclears, 3 per cent; eosinophils, 5 per cent, and basophils, 1 per cent. The Wassermann reaction of the blood was negative.

A biopsy of one of the nodules of the right leg revealed perivascular infiltration of round cells with chronic inflammatory changes.

The wound from the biopsy did not bleed freely, but there was a large amount of seepage of serum that was almost as tenacious as mucilage.

DISCUSSION

DR. UDO J. WILE: I have never seen anything quite like these lesions, but wish to call attention to the verrucose type of lesions resembling those seen in other parts of the body, chiefly around the neck and the scalp. Since the lesions followed a thyroidectomy, the possibility that they may be myxedematous should be definitely substantiated by determining a myxedematous condition of the patient as well as a myxedematous structure in the lesion itself. As I recall the myxedematous changes in the skin that I have seen, they have been soft lesions and not indurative. In this case the myxedema, if it is that disease, is extremely board-like. I think that the suggestion is a happy one.

DR. J. H. MITCHELL: The condition of the legs suggested that the disease is possibly a low grade infectious lymphangitis.

DR. S. W. BECKER: I think that this is a localized myxedema. The case illustrates the peculiarities encountered in the hyperthyroid syndrome. It is possible to have this picture following thyroidectomy, with hyperthyroidism. The workers in hyperthyroidism have not yet been able to explain either these various combinations or the chemical deposits in the skin.

DR. O. H. FOERSTER: Those of us who were in Copenhagen may recall a patient with myxedema in the presence of hyperthyroidism, presented by Dr. Galewsky of Dresden. That case bears out what Dr. Becker has said. There was a diffuse type of infiltration rather than the nodular type such as in the case under discussion.

DR. E. A. OLIVER: We discovered this case accidentally Monday afternoon in the eye clinic and will do further work on it, but we thought that it was sufficiently interesting to present today. The patient still has considerable exophthalmos, but he has no tachycardia and is not at all nervous. I took his pulse after he was presented today and it was 72. While he may have hyperthyroidism, with these symptoms I doubt it. I will see that the basal metabolic rate is taken and will try to report at the next meeting, for I think that the case is interesting.

DR. RUBEN NOMLAND: I saw one of the patients in Dr. O'Leary's series. He had been operated on for goiter and still had exophthalmos. Later the plaques on the legs developed which were considered as localized myxedema.

(Three estimations of the patient's basal metabolic rate were: plus 9, minus 10, minus 11.)

A Case for Diagnosis (Scleroderma? Herpes?). Presented by Dr. S. W. Becker.

A woman, aged 27, a housewife, was cut over the left eye in an automobile accident four years previously. Soon after this, an eruption occurred which was similar to "prickly heat." This eruption had recurred at times since then.

The results of a physical examination were generally negative. Neurologic examination showed diminution of sensation to pain and touch in the region of the eruption. The diagnosis was that of an apparently cured traumatic neuritis, with inflammation due to irritation of a cell group of the gasserian ganglion.

The skin was somewhat oily and the scalp was scaly. Over the left eye was a linear transverse scar about 2 cm. long. Extending from a short distance below this to somewhat within the hair line, and from within outward, was an eruption consisting of punctate crusts, scars and hyperpigmentary macules.

DISCUSSION

Dr. F. E. Senear: I have no definite diagnosis to offer, but I feel that in the involved area there was definite pigmentation; the skin was of lighter color there than elsewhere on the forehead. I think that it might be an atypical scleroderma like that reported following trauma.

Dr. O. H. Foerster: It occurred to me that the minute vesicles developed on a neuritic basis, possibly as an after-effect of an injury, and were perhaps related to the automobile accident that was mentioned. The history of continuous recurrence was the prominent feature in a similar instance that I saw in which, following extraction of the teeth, a group of minute vesicles covering a dime-sized area on the chin recurred daily for two years in association with hyperesthesia and neuritic pain.

Dr. S. W. Becker: We could not make a definite diagnosis of herpes, but we did notice, as Dr. Senear mentioned, that the affected side seemed to be somewhat fuller than the rest of the forehead. Two years ago I read the literature rather extensively in an effort to find cases of diseases of the skin following injury of the peripheral nerves. It is surprising how few cases are reported in the literature.

A Case for Diagnosis: Blue Nevus? Presented by Dr. M. H. Ebert and Dr. Ruben Nomland.

A girl, aged 23, had first noted pigmentation on the sclera of her left eye eight years previously. In the beginning it was similar to the condition starting in her right eye. About three years before presentation pigmentation had first appeared on her left temple and had spread slowly since that time. She used no cosmetics except rouge and powder. During the past three years, after the pigmentation had begun on her face, she had worked at a wrapping machine, using tinfoil.

She presented a bluish-black pigmentation of the lower half of the sclera of the left eye. It was sharply marginated where it stopped, about 1 mm. from the cornea. The right eye had a similar but lighter and less extensive pigmentation beginning at the inner margin near the cornea, but separated by an unpigmented space. The skin about the region of the left temple and the left eyelid was the site of a bluish-gray, slightly mottled pigmentation with rather definite margins, about 10 by 8 cm. in size.

A biopsy of the pigmented region of the temple showed no change in the epidermis and no increase in pigment. There was increased pigment in the midcutis. It consisted of elongated cells ranged parallel to the surface and containing large brown pigment granules. There were a few pigment-bearing cells in the upper cutis.

From the location and the nature of the lesion and the reaction to staining with polychrome methylene blue (methylthionine chloride, U. S. P.) the pigment

was apparently melanin. There were no indications of granules around the sweat glands even on dark field illumination.

DISCUSSION

DR. S. W. BECKER: The histologic section is that of a blue nevus. I think that it is too deep for pigment-carrying cells.

DR. M. H. EBERT: I think that before we make a final diagnosis we should do a biopsy so that we may know definitely whether the deep cells are melanoblasts or are simply pigment-carrying cells.

TUBERCULOSIS CUTIS: MULTIPLE SARCOIDS. Presented by DR. M. H. EBERT and DR. RUBEN NOMLAND.

A well nourished Negress, aged 40, consulted an eye clinic three years ago for a condition on the skin of her left eye that had been present for several months. A piece was removed and a blood test was taken. After this she received a course of antisyphilitic treatments lasting six months, but there was no improvement in the condition. After several months of rest she received another course of injections and still later, a third course. At one time she was told that her blood was "bad" (++++). She stated that she had a "sore on her privates" in 1912. She had had one miscarriage, and one child died at the age of 8 days.

In spite of the rather intensive antisyphilitic treatment, the lesions on her face enlarged and new ones appeared on the chin, nose, the other eye and the nasolabial folds. About a year previous to presentation, deeper lesions appeared on the extremities and the body. They all began as nodules of various sizes in the skin, that slowly enlarged and cleared in the center, but did not disappear completely.

This woman presented several types of lesions. On the face, eyelids, nasolabial folds, nose and chin were flat lesions made up of papules about the size of a match-head and arranged in annular form. On the back of the neck, especially, there were several dozen isolated lesions that were lichenoid, discrete papules. On the arms, body and legs were several dozen annular lesions and nodules. The nodules, when discrete, were pea-sized and larger. In many places there were annular lesions composed of nodules of varying sizes and depths, the center being depressed but not scarred, and the periphery indurated. Some of these annular lesions were over 4 cm. in diameter. There was no ulceration, although she stated that a few lesions had broken down.

The Wassermann reaction had been negative on two occasions, the latter after a provocative procedure. She had had three injections of 0.3 Gm. of neoarsphenamine with no objective improvement, although she stated that the lesions had improved. She refused a specimen for biopsy.

One of the small lichenoid lesions from the back of the neck was removed for microscopic examination.

It showed slight atrophy of the epidermis with almost complete lack of pigment in the basal cell layer, an unusual condition in a Negress. The subpapillary region was the site of a well circumscribed tuberculoid area consisting of many giant cells and epithelioid cells. In the deeper cutis were sharply circumscribed areas of infiltration separated by bands of connective tissue. The infiltration consisted mostly of epithelioid cells with a few lymphocytes in the adjacent stroma. It was a fairly typical sarcoid structure.

DISCUSSION

DR. E. P. ZEISLER: I agree with the diagnosis of multiple sarcoid. The patient has also the lesions of lupus disseminatus milius which may coexist with sarcoid.

DR. UDO J. WILE: I should not accept the diagnosis of sarcoid on this patient without a typical histologic picture of that disease. There were at least thirty-five typical cases of sarcoid and tuberculosis at the Congress in Copenhagen, and

all of us who saw them were impressed with the fact that they in no way resembled cases of this kind. They were all cases of plaquelike indurated tumors, usually on the face. This case is almost a counterpart of one that was presented last week in St. Louis, in which the diagnosis of sarcoid was made. I think that we are subjecting sarcoid to a great deal of confusion and departing from the original description of the disease. In the first place, sarcoid is a poor name for any disease other than sarcoma. When we speak of cases of sarcoid-like nature I think that there is no excuse whatever for such nomenclature. I believe that the whole chapter on cutaneous tuberculosis has to be rewritten. The picture that conforms to that of sarcoid, which is referred to here, is a noncaseated, encapsulated multiple tuberculous structure that can occur anywhere, but that usually occurs on the face. I think that biopsy in this case will show it to be a cutaneous tuberculosis of disseminated character. If so, I think that is the best name for it.

DR. J. H. MITCHELL: I agree with Dr. Wile, and I am inclined to think that all these so-called sarcoids are tuberculous.

DR. M. H. EBERT: I think that Dr. Wile was correct in his statement that a final diagnosis of sarcoid cannot be made without presentation of a histologic specimen showing the so-called sarcoid structure. However, clinically I was impressed with the idea that the lesions on the trunk and back corresponded to the type described by Darier-Roussy, and I thought that the lesions on the face might correspond with the superficial, nodular type of sarcoid. I think that we can perform a biopsy, but we probably will not see the patient afterward.

DR. RUBEN NOMLAND: In October, 1929, (Oliver, E. A.: Sarcoid, ARCH. DERMAT. & SYPH. **22**:173 [July] 1930), Dr. Oliver presented a patient with lesions on the face analogous to those presented by this woman. Two or three biopsies that were performed in that case showed the typical sarcoid structure. Several years ago Dr. Mitchell took pictures of that patient and they appear in Dr. Ormsby's textbook as illustrations of a case of tuberculosis cutis disseminatus (Buzzi). Microscopically the lesions were sarcoid and that is why we had the temerity to call this condition a sarcoid.

DR. O. H. FOERSTER: The lesions on the neck in this woman are the counterpart of the lesions in Carroll Wright's case described recently under the name of "lichenoid sarcoid."

DR. E. P. ZEISLER: All the cases shown in Copenhagen were in white persons. The disorder is quite different in the Negro.

PERIFOLLICULITIS CAPITIS ABSCEDENS ET SUFFODIENS. Presented by DR. F. E. SENEAR and DR. M. R. CARO.

A Negro, aged 46, had an eruption that began about ten months previously, after he had taken four bottles of a patent medicine for his blood. A few pimples broke out on the back of the scalp and on the face and back. After he had shaved his scalp, itching and nodules appeared over the entire scalp.

Nearly all of the scalp, especially the occipital and parietal regions, was covered by large boggy fluctuating masses which seemed to undermine the scalp, and from which thin pus exuded on pressure. On the face there were a number of indurated acne pustules, and a few were present on the back.

The patient had shown some improvement after daily applications of a solution of bichloride of mercury (1:1,000) and ammoniated ointment of mercury.

DISCUSSION

DR. MAX S. WIEN: In the discussion of Barney's report at the Detroit session of the American Medical Association, Dr. Wise commented on the fact that he had never seen a case of this type in a Negro. This is the second case that we have had in Dr. Senear's clinic in the past two years and both were in Negroes.

CLEVELAND DERMATOLOGICAL SOCIETY

H. J. PARKHURST, M.D., *Reporter*

Regular Meeting, Dec. 18, 1930

J. R. DRIVER, M.D., *Presiding*

LICHEN PLANUS. Presented by DR. R. E. BARNEY.

Mrs. I. R., aged 41, had been under treatment for a latent syphilitic infection since September, 1925. Since 1922, she had noticed an asymptomatic eruption on the wrists and dorsa of the hands. It had first appeared during the course of what seemed to be a dermatitis caused by arsphenamine, while she had been under the care of another physician.

On the dorsa of the hands, flexures of the wrists and to lesser extent on the flexor surfaces of the forearms, there was an eruption consisting of purplish-gray lesions varying in size from that of a pinhead to that of a small pea. Some of the lesions were distinctly papular, angular, flat-topped, shiny and umbilicated, and occasionally adherent scales were present. Some of the lesions were atrophic.

One of the atrophic lesions showed the following histologic picture: The epidermis was thin, and the rete pegs were flattened. The papillary layer of the corium showed fibrosis with a moderate perivascular lymphocytic infiltration.

LICHEN PLANUS ATROPHICUS. Presented by DR. R. E. BARNEY.

S. V., a laborer, aged 37, complained of generalized pruritus of six weeks' duration. A sulphur ointment had been applied. An eruption composed of two types of lesions involved chiefly the cubital fossae, the inner aspects of the thighs and to a lesser extent the trunk, genitalia, buccal mucous membrane and forearms. One type of lesion consisted of dime-sized to half dollar-sized groups of smaller lesions and varied from the size of a glass pinhead to that of a large pea. These lesions were atrophic and subacutely inflammatory, and their borders were sharply demarcated, presenting a white line. The bases were made up of thinned purplish epidermis, with fine reticulation. This type of eruption was found in the cubital fossae, at the back of the neck and over the right side of the chest, but chiefly on the inner aspect of the right thigh. There were white, atrophic lesions, the size of a glass pinhead, on the dorsal surface of the prepuce and on the scrotum. The second type of lesion was a white, flat-topped, angular, umbilicated papule, varying in size from that of a small pinhead to that of a glass pinhead; these papules were scattered over the trunk and extremities, being most numerous in the cubital fossae. There was also a large pea-sized, purplish papule with a central caseous plug in the right axilla, and a glass pinhead-sized, gray papule was found in the left buccal mucosa. There was a marked, bilateral, pea-sized to cherry-sized, shotty, painless, inguinal and axillary lymphadenitis. The Wassermann reaction of the blood was negative.

A specimen for biopsy was taken from one of the atrophic lesions on the chest. The epidermis was moderately hyperkeratotic; the rete pegs were flattened. One follicular opening showed a hyperkeratotic plug. The major pathologic process was situated in the papillary layer of the corium, where there was marked fibrosis. Masson's stain showed a reticulum of fibers running roughly perpendicular to one another. In this network were numerous macrophages containing a brown granular pigment, probably hemosiderin, and a moderate lymphocytic infiltration. There were also increased vascularity and fibroblastic proliferation. The elastic tissue was almost entirely absent in the area corresponding to the infiltrate.

DISCUSSION

DR. C. B. NORRIS: At first glance, the eruption involving the ears, genitalia and cubital fossae suggested an allergic dermatitis, but undoubtedly it was caused

by the sulphur and blue stone used locally. Closer study of the fine white lesions and atrophic areas confirmed the diagnosis of atrophic lichen planus.

DR. E. W. NETHERTON: I agree with the diagnosis. This case, together with the other cases of lichen planus that have been presented, shows the various forms that lichen planus may take. The observations from the biopsy are interesting.

A CASE FOR DIAGNOSIS (SCLERODERMA?). Presented by DR. CLAUDE B. NORRIS.

N. M., an Italian boy, aged 12, had first been observed on Oct. 31, 1930, with a condition of about one year's duration. At that time there had been redness, edema and dryness of the eyelids and the entire face, the swelling being pronounced. All over the body there were subcutaneous infiltration and edema, involving not only the deeper structures of the skin, but the subcutaneous structures and the musculature, the latter being tender on movement. The feet were greatly swollen. There was considerable pigmentation, and in areas some depigmentation. Slight improvement was apparent at the time of presentation. There had been a considerable loss of weight.

DISCUSSION

DR. SIDNEY LITTMAN: There appear to be three possibilities in this case: scleroderma, dermatomyositis or trichiniasis. The edema is deeper than the skin and involves the muscles, which are tender. There is an apparent contracture of the biceps, and radiographic studies of the joints of the elbows might reveal infiltration.

This case corresponds to one that I observed recently, in which the possibility of dermatomyositis was considered. In that case there was a peculiar eruption. The eruption on the hands resembled pellagra and that elsewhere psoriasis. The picture was much the same as in the present case. The condition was found to be trichiniasis. It would be important to know whether this patient has been febrile at any stage. The salient feature seems to be a myositis rather than a dermatitis.

DR. H. G. MISKJIAN: The question of fever is important in the diagnosis of trichiniasis. To me the diagnosis of scleroderma seems logical. In extensive cases of scleroderma there are pigmentary disturbances, as presented here, and the edema is not against scleroderma, even though the muscles and deeper structures are involved. In its early stages, scleroderma, if it is generalized as in this case, may involve the muscles.

DR. R. E. BARNEY: There is a tremendous disturbance of the metabolism in this case, as is shown by the pigmentary disturbances and the widespread involvement. To me this eruption suggests lupus erythematosus. There is follicular atrophy, and the lips and buccal mucosa are involved. The induration is too deep for scleroderma. I should suggest radiographic studies of the elbows to determine whether there is involvement of the bones and joints. It seems that the muscles are affected more than the skin.

DR. J. R. DRIVER: Does Dr. Barney have reference to disseminated lupus erythematosus?

DR. R. E. BARNEY: I do not consider the condition disseminated lupus erythematosus, because the patient is not sick enough.

DR. J. R. DRIVER: The fact that the patient is hidebound, the areas of vitiligo and other features lead one to suspect scleroderma. In this condition one often finds the sclerotic process more than skin deep.

DR. J. E. FISHER: The edema and the hidebound condition suggest scleroderma.

DR. E. W. NETHERTON: I agree with Dr. Barney. There is a striking tenderness of the muscles, and edema rather than a sclerotic process. It would be interesting to know exactly what has been included in the patient's diet.

DR. H. J. PARKHURST: My reaction is similar to that of Dr. Barney. The lesions on the nose and eyelids seem to be subsiding.

DR. C. B. NORRIS: I have no definite knowledge of the patient's diet, but shall try to ascertain whether it has included pork or wild game. I have felt that scleroderma was most likely the correct diagnosis and have prescribed thyroid extract and cod liver oil, together with local emollients and a small amount of fractional roentgen irradiation. The swelling of the feet has subsided, the skin is softer, and the general health is better.

LUPUS MILIARIS DISSEMINATUS FACIEI. Presented by DR. E. W. NETHERTON.

A married man, aged 22, a printer, who was well developed and well nourished, gave an apparently irrelevant past history. He had apparently had acne for several years, but two months before the time of presentation crops of somewhat different lesions had appeared in the midportion of the face. The lesions had persisted. The nose, forehead and chin were involved, and there were also isolated lesions scattered over the rest of the face and a few on the shoulders and back. Most of the lesions were grouped papules, varying in size from that of a pinhead to that of a match-head, and some showed central pustulation. None was associated with comedones, and some presented slight adherent central scaling and crusting. Apple jelly-like nodules could be demonstrated under diascopic pressure. On the chin and between the brows, the lesions had become confluent, with diffuse nodular infiltration in places. On the chin and in one or two places on the upper lip, there were some vegetating areas, but no exudate. There were also several small pitted scars on the face, and a few acute pustules of acne. Radiographic studies of the chest showed the presence of considerable hilar fibrosis in both lungs, the diagnosis being "old bronchitis." Histologic examination showed the presence of tubercles, with necrosis in the derma. No bacilli had been found after a prolonged search through stained sections.

DISCUSSION

DR. H. G. MISKJIAN: I am impressed with the somewhat confluent, vegetating condition of the chin, while on the nose and other portions of the face the lesions are discrete papules. The presence of numerous apple jelly-like nodules reveals their tuberculous nature. The diagnosis of disseminated miliary lupus fits the case, but the vegetating lesions show how difficult it sometimes is to put some of these cases of tuberculosis into a definite group. The existence of transitional types must be admitted.

DR. E. W. NETHERTON: I think that this is a case of miliary lupus and that the prognosis is not good. I intend to use gold sodium thiosulphate, proceeding cautiously.

DR. J. R. DRIVER: I recall one other case in a woman, who benefited by filtered roentgen irradiation. Gold sodium thiosulphate may prove beneficial, but must be used cautiously.

TERTIARY SYPHILIS AND TATTOOING. Presented by DR. JOHN A. GAMMEL.

An ex-soldier, aged 35, with extensive tattooing of the forearms, had noticed nodular lesions on the right forearm for six years. Some of the lesions had healed, others had broken down, and new lesions had developed. He had had a chancre and a positive Wassermann reaction in 1921, and at that time he had received eight injections of neoarsphenamine and eight of a mercurial compound. When first observed at the Lakeside Hospital on Dec. 1, 1930, he presented a crusted lesion on his back and two punched-out ulcers of small coin-size on the flexor surface of the right forearm, adjoining a group of papular lesions. While the lesions had destroyed part of the tattoo marks, they had not invaded the areas colored with red (cinnabar). Two injections of arsphenamine and potassium iodide had been given, and the lesions were rapidly disappearing.

DISCUSSION

DR. M. J. GIBANS: This case shows that cinnabar remains permanently antisyphilitic.

DR. J. R. DRIVER: A similar observation was made by Dr. Wile in a patient with papular syphilis.

MINNESOTA DERMATOLOGICAL SOCIETY

D. D. TURNACLIFF, M.D., *Secretary*

Regular Meeting, Dec. 19, 1930; Ancker Hospital, St. Paul

EDWARD C. GAGER, M.D., *President, Presiding*

GRANULOMA ANNULARE. Presented by DR. C. D. FREEMAN.

Miss S. presented lesions that began one year before presentation on the right elbow as deep-seated infiltrations of the skin. Her past history was unimportant. At the time of presentation there were lesions on both arms and on the right thigh. The nodules were not crescentic or circinate, but were more or less irregularly arranged, and involution had taken place in some of the lesions. The biopsy specimen showed a decided cellular infiltration with lymphocytes, polymorphonuclear leukocytes and proliferative connective tissue cells in the subpapular layer. Necrosis was present in the center of some of the infiltrated areas.

The patient's father and mother died of tuberculosis, the mother having contracted it from the father. Her brothers and sisters were well.

DISCUSSION

DR. C. D. FREEMAN: When I first saw the case I thought that the condition was sarcoid, but a diagnosis of granuloma annulare was returned from the University of Minnesota where the biopsy specimen was sent for examination. It is not typical, however, of granuloma annulare.

A CASE FOR DIAGNOSIS. Presented by DR. C. D. FREEMAN.

Miss P., aged 20, with an unimportant past and familial history, stated that the present illness began in April, 1930. She presented a sharply demarcated, markedly symmetrical keratosis of both palms and soles, which was negative for fungus. Biopsy showed a mild hyperkeratosis. There was no change in other parts of the epidermis, corium or blood vessels. There were no other lesions on the body. It was necessary to make a differential diagnosis between pityriasis rubra, psoriasis, acquired keratosis palmaris et plantaris and mycelial infection, but the biopsy was suggestive of keratosis of the acquired type.

DISCUSSION

DR. J. F. MADDEN, St. Paul: This case has been altered a good deal by treatment. After roentgen treatments the hyperkeratosis was cut down from 200 to 300 per cent. Fresh preparations and cultures were negative for fungi. I think that this is an example of the acquired type of keratoderma palmaris et plantaris.

DR. JOHN BUTLER, Minneapolis: I have never seen a case of palmar psoriasis that did not show some involvement of the nail-bed or changes in the nail.

DR. S. E. SWEITZER, Minneapolis: In this particular case I think that we must consider several possibilities. One is palmar keratosis, another is psoriasis of the palms, another is pityriasis, and still another is the possibility of ringworm. The condition as it presents itself looks very much like pityriasis rubra pilaris, but the fact that Dr. Wright found a small lesion on the back of the hand with a silvery scale, inclines me to believe that it is psoriasis.

ADENOMA SEBACEUM. Presented by DR. JOHN F. MADDEN.

All of the cases presented by Dr. Madden at this meeting were from the service of Dr. H. N. Klein and Dr. J. F. Madden at Ancker Hospital.

I. E., aged 14, presented an eruption of pinkish, from pin-head to split-pea sized papules associated with telangiectasia, and confined to the face, nose, naso-labial folds and chin. The lesions were soft and apparently not inflammatory. The patient had had convulsions daily for the past three weeks. He had spent two years at the Home for the Feeble Minded in Faribault. There were numerous associated nevi, pigmented and otherwise, over the entire cutaneous surface. Several Wassermann tests of the spinal fluid gave negative results, and the Wassermann reaction of the blood was negative. The blood sugar was normal; hemoglobin, 95 per cent; red blood cells, 5,340,000, and white blood cells, 14,300.

DISCUSSION

DR. J. F. MADDEN: There seems to be some question as to the connection between the lesions in the skin and the other symptoms in this patient. I went over the cases of adenoma sebaceum reported in the literature, and found that the original description was made by Balzer, in French, in 1885. Shortly after that Addison, in England, described the disease, and in a few years (1893) it was described by Politzer in this country. Since then there have been a great number of articles, and all of them agree that adenoma sebaceum is a developmental anomaly found in the skin alone. There was only one dissenting article and that was by Olson, in 1922, in which he stated that sometimes lesions histologically similar appear in the heart and other organs of the body. He showed no photographs or photomicrographs to support his contention, and quoted no authorities to uphold it. The only similarity between adenoma sebaceum, nevi and the lesions described by Olson are that they are all developmental anomalies.

LUPUS ERYTHEMATOSUS. Presented by DR. H. N. KLEIN.

The patient, a schoolgirl, aged 12, had a typical eruption on the face which started at the age of 9 years.

DISCUSSION

DR. H. N. KLEIN: The skin picture is typical of lupus erythematosus, but one interesting factor is the age of the patient.

DR. F. R. WRIGHT, Minneapolis: I would like to ask if it is not an interesting proposition that lupus erythematosus should develop in a child at the age of 9 years. The patient is now 12 and has had the disease for three years. My impression has always been that lupus erythematosus was a disease of adult life rather than of childhood.

DR. S. E. SWEITZER: I should like to call attention to a recent article in *The Journal of the American Medical Association* on the observations made on the blood in patients with these skin lesions. We are trying to do some work at the University of Minnesota along this line and we would like a specimen of the blood from this child. Dermatologists have been conducting similar experiments in Vienna, and find that quite a large percentage of the cases of lupus erythematosus have tubercle bacilli in the blood.

BLASTOMYCOSIS. Presented by DR. JOHN F. MADDEN.

Mrs. F. H., aged 51, a housewife, first noticed a dime-sized, warty growth on the nose and right cheek in April, 1930. This was followed in a short time by soft, fluctuant nodules about the size of a hickory-nut on the right elbow and right forearm. The right ankle became swollen and painful in June, 1930. A roentgen examination disclosed destruction of the astragalus and lower end of the tibia. There was an accompanying destruction of the proximal ends of the right tibia and fibula. Roentgen examination of the chest in September, 1930, exhibited

an infiltration of the apex of the right lung. Blastomycetes have been demonstrated in fresh preparations.

DISCUSSION

DR. J. F. MADDEN: The most interesting feature in this case is the recent improvement under strenuous treatment, i. e., large doses of neoarsphenamine intravenously, 180 grains (11 Gm.) of potassium iodide daily, cautery to the lesions and roentgen therapy.

DR. J. BUTLER: Would there be just as much benefit if the neoarsphenamine was stopped and more iodide given?

DR. J. F. MADDEN: During the past four months at the University Hospital we have had two or three patients with pulmonary involvement. When admitted they were in very poor condition. We gave them this intensive combined therapy, and they are all home and working now.

DR. S. E. SWEITZER: I had a patient with blastomycosis recently to whom I gave potassium iodide and roentgen treatment. The patients with pulmonary lesions usually die.

DR. J. F. MADDEN: More cases of blastomycosis are probably seen in Chicago than anywhere else in the world. Several dermatologists there use the method of therapy that I have outlined as a routine measure. Since they have given patients with this disease more intensive treatment their results have improved greatly.

A CASE FOR DIAGNOSIS. Presented by DR. JOHN F. MADDEN.

A. C., aged 36, colored, a laundress, stated that in July, 1929, she noticed a sore throat and difficulty in hearing. In spite of local treatment the sore throat progressed, and in November, 1929, she noticed a tumor in the right axilla, accompanied by pain and numbness of the right hand. The right arm became extremely swollen in its entire length. On Feb. 22, 1930, physical examination disclosed perforation of the soft palate, a swelling of the right arm, extending throughout its entire length, accompanied by pitting edema. The patient had been treated for syphilis constantly since February, 1930.

At the time of presentation the right arm presented a globular, firm, painless tumor which seemed to be attached to either the bone or periosteum. The Wassermann reaction of the blood was strongly positive in February and negative in April, 1930. Roentgen examination disclosed no involvement of the bones; however, on Nov. 20, 1930, a roentgen report stated that there was marked atrophy of the right humerus, but no signs of localization.

DISCUSSION

DR. F. R. WRIGHT: The patient undoubtedly has syphilis in the mouth. The condition on the arm may be due to an entirely different condition. I think the patient unquestionably has syphilis.

DR. S. F. MADDEN: There was some discussion that the lesion on the arm might be a fibrosarcoma. A biopsy will be done and reported on.

IDIOPATHIC ATROPHY OF THE SKIN. Presented by DR. E. C. GAGER.

A woman, aged 50, presented the classic appearance of atrophy of the skin of both legs. The skin was white and finely wrinkled, and the venules could be seen under the skin. The duration of the condition was ten years.

PRIMARY SYPHILIS, CHANCRE OF THE THIGH, SECONDARY SYPHILIS AND PAPULOSQUAMOUS LESIONS OF THE PALMS. Presented by DR. JOHN F. MADDEN.

Mrs. O. M. M., aged 27, a housewife, first noticed the lesion on the thigh and those on the palms of the hands about Dec. 8, 1930. On December 15, she

delivered a premature baby, which died soon after birth. At the time of presentation the lesion on the medial surface of the left thigh just below the external genitalia was a dime-sized, indurated, painless, eroded papule with a hemorrhagic border from which serum was easily expressed. *Spirochaeta pallida* was demonstrated from this lesion. The lesions on the palms were from pea to bean-sized, indurated, painless papules covered with a dry scale, many of which had formed circles or parts of circles. The Wassermann reaction of the blood was strongly positive.

A CASE FOR DIAGNOSIS. Presented by DR. JOHN F. MADDEN.

E. G., aged 33, a laborer, stated that he noticed an eruption on the thenar and hypothenar eminences of both hands about ten months prior to presentation. The lesions covered these areas and exhibited a faint erythematous center and a very bright erythematous periphery. They were asymptomatic. The patient had advanced pulmonary tuberculosis, with consolidation of the upper lobe of the right lung. The eruption had not changed since it had first appeared. Biopsy gave negative results.

A CASE FOR DIAGNOSIS. Presented by DR. JOHN F. MADDEN.

Mrs. T. F., aged 40, a housewife, stated that she noticed an eruption on the thenar and hypothenar eminences of both hands about one year prior to presentation. The lesions practically covered these areas and presented an erythematous center and a very bright erythematous border. There were no symptoms and no associated scales. The patient had advanced pulmonary tuberculosis with cavities in both lungs. The eruption had not changed since it first appeared.

A CASE FOR DIAGNOSIS. Presented by DR. JOHN F. MADDEN.

L. M., aged 40, a laborer, stated that he first noticed an eruption on the thenar and hypothenar eminences of both hands about ten months prior to presentation. The lesions covered these areas and presented a faint erythematous center and a very bright erythematous periphery. The patient had advanced pulmonary tuberculosis with extensive cavities in both lungs. The eruption had not changed since it first appeared.

A CASE FOR DIAGNOSIS. Presented by DR. JOHN F. MADDEN.

Mrs. A. K., aged 48, a housewife, stated that she first noticed an eruption on the thenar and hypothenar eminences about four months prior to presentation. The eruption pained and itched when she got warm. The eruption consisted of erythematous patches confined to the areas described. The border was a much brighter red than the central portions of the lesions. The patient had a collapsed left lung and advanced pulmonary tuberculosis. The eruption had not changed since the first appearance. A biopsy of the lesion revealed no pathologic change.

DISCUSSION

DR. J. F. MADDEN: These cases definitely are not lupus pernio. Microscopically they show little more than dilatation of the superficial vessels. I asked Dr. Klein and Dr. Michelson to look at the patients previously, and they had not seen similar cases.

DR. F. R. WRIGHT: The disease is simply an erythema due to some local irritation; at least that is what it looked like to me.

DR. J. F. MADDEN: The eruption developed in two of the patients before they were hospitalized, in one of them four months, and in the other an unknown length of time before hospitalization. Two of the cases occurred before and two after the patients came to the hospital.

We thought of a possible phthalein eruption, but on close questioning, we found that the patients had not received medication of any kind.

PYOGENIC GRANULOMA. Presented by DR. JOHN F. MADDEN.

Mrs. E. N., aged 33, a housewife, stated that she had had calluses on the balls of her feet for some time. In April, 1930, these lesions became somewhat painful, and she began soaking her feet in hot boric acid solution and paring down the lesions. In June, 1930, she noticed that the lesions had become soft in the center and were draining a purulent fluid. The central portions of the lesions became ulcerated, and later globular nodules appeared in the center of each ulcer. The nodules bled easily and became very painful. The lesions were cauterized with actual cautery on December 3, and one of them had healed at the time of presentation.

The patient also had tabes dorsalis with a negative Wassermann reaction of the blood and a 4 + Wassermann reaction of the spinal fluid.

NODULO-ULCERATIVE SYPHILID (ARMS) AND HEALED GUMMAE OF THE LARYNX. Presented by DR. JOHN F. MADDEN.

Mr. F. A., aged 54, a cook, stated that he contracted a primary penile lesion in 1922. One year later he noticed small ulcers appearing on the right arm and elbow. About this time he became hoarse.

At the time of presentation, the lesions on the arm were deep-seated, painless, confluent, bean-sized papules, presenting an arcuate formation. Most of those on the right forearm exhibited atrophic scarring, except near the elbows and wrists where the lesions that have been described existed. The patient had taken 1/8 grain (0.008 Gm.) of iodide of mercury, four times a day for the past seven years, and had used an occasional mercury rub. On laryngoscopic examination, Dr. Strate demonstrated a marked atrophic scarring of the larynx. The Wassermann reaction of the blood was strongly positive.

ACNE KELOID. Presented by DR. H. N. KLEIN.

A man, aged 22, had had an eruption of nodular lesions on the back of the neck for two years prior to presentation.

DISCUSSION

DR. S. E. SWEITZER: I think that the recognized treatment for acne keloid is roentgen therapy. Dr. Freeman said that he would be afraid of provoking a permanent epilation of the hair with such treatment, but I think that it could be avoided in this case.

SUBCUTANEOUS FIBROID SYPHILOMAS, JUXTA-ARTICULAR TYPE. Presented by DR. H. E. MICHELSON.

A man, aged 35, had several nodes in the vicinity of the elbow joint that had been present for a number of years. The history for syphilis was negative, and the Wassermann reaction was repeatedly negative. A node was excised, which showed a deep-seated infiltrate arranged in whorls surrounded by dense fibrous tissue. The microscopic diagnosis was fibroid syphiloma. Under antisyphilitic treatment the nodes diminished in size but did not disappear.

DISCUSSION

DR. D. D. TURNACLIFF: When I first saw the patient he had several periosteal lesions on the ulna which have subsided, and I believe the original skin lesions have decreased one-half.

DR. S. E. SWEITZER: These fibromata when really due to syphilis are very rare. We have had only one case presented before this society. At present I have one at the General Hospital with typical subcutaneous nodules along the ulnar area. The point in treatment was that they were not gumma and either did not respond to antisyphilitic therapy, or responded but slowly. I think that the most rapid way to get rid of these is to remove them surgically. Jeanselme described a condition called juxta-articular nodes that resembles this.

I think that there is some doubt that these syphilomas are due to syphilis, for they do not respond to antisyphiltic treatment. Our patient had lesions as large as a marble which did not involute readily under antisyphilitic treatment. There was some question as to whether these were the same as the juxta-articular nodes, but I do not believe that it was settled.

DUHRING'S DISEASE. Presented by DR. C. D. FREEMAN.

DISCUSSION

DR. C. D. FREEMAN: I was wondering if any of the members had had any experience in these cases with roentgen treatment of the spine.

DR. S. E. SWEITZER: Dr. Winer said that Oppenheim of Vienna has a much better treatment than the ordinary arsenic for these cases, which is acetarsone. This is also an arsenical product.

DR. E. C. GAGER: I tried roentgen treatment of the spine in a case of dermatitis herpetiformis that I reported before this society some time ago. The patient became well and I have not seen him since. I do not know whether or not the roentgen treatment was responsible for his cure, but all of his lesions cleared up. I do not recall the exact dosage, but it was the regulation dosage used over the spine.

DR. F. R. WRIGHT: For years arsenic has been used for all chronic lesions of the skin. When we change to neoarsphenamine and obtain results, it simply means that by using it we can get the largest amount of arsenic into the system with the least disturbance. Neoarsphenamine is 23 per cent arsenic. In these cases I think that the improvement is due to the quantity of arsenic rather than to the special preparation.

DR. E. C. GAGER: I would try four-fifths of a skin unit filtered through aluminum applied above the scapula, below the scapula and in the lumbar region and see what effect it would have. The patient I spoke of became absolutely well.

Directory of Dermatologic Societies *

NATIONAL DERMATOLOGIC SOCIETIES

American Medical Association, Scientific Assembly, Section on Dermatology and Syphilology

Elmore B. Tauber, Chairman, 19 W. 7th St., Cincinnati.
Francis E. Senear, Secretary, 55 E Washington St., Chicago.
Place: Philadelphia. Time: June 8-12, 1931.

American Dermatological Association

C. Morton Smith, President, 437 Marlboro St., Boston.
W. H. Guy, Secretary, 500 Penn Ave., Pittsburgh.
Place: Toronto. Time: June 15-17, 1931.

British Association of Dermatology and Syphilology (Canadian Branch)

Emerson J. Trow, President, Medical Arts Bldg., Toronto.
Hamnett A. Dixon, Secretary, Medical Arts Bldg., Toronto.
Place: Toronto, Ontario, Canada. Time: June, 1931.

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* Secretaries of dermatologic societies are requested to furnish the information necessary for the editor to make this list complete and to keep it up to date.

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Howard Morrow, President, 384 Post St., San Francisco.
John M. Graves, Secretary, 909 Hyde St., San Francisco.

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